IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NATERA, INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 20-125 (LPS)
	)	(CONSOLIDATED)
ARCHERDX, INC., ARCHERDX, LLC and INVITAE CORP.	)	
	)	**JURY TRIAL DEMANDED**
	)	
Defendants.		

SECOND AMENDED CONSOLIDATED
COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Natera, Inc. ("Natera"), for its Second Amended Consolidated Complaint against defendants ArcherDX, Inc., ArcherDX, LLC ("Archer") and Invitae Corporation ("Invitae") (collectively, "Defendants"), hereby alleges as follows:

OVERVIEW OF THE ACTION

1. This is a consolidated patent infringement action brought under 35 U.S.C. § 271 arising from Defendants' infringement of Natera's United States Patent No. 10,538,814 ("the '814 patent"), United States Patent No. 10,557,172 ("the '172 patent"), United States Patent No. 10,590,482 ("the '482 patent"), United States Patent No. 10,597,708 ("the '708 patent") and United States Patent No. 10,731,220 (the "'220 patent") (collectively, the "Asserted Patents"), by the manufacture, use, sale, and offer to sell of Archer's LiquidPlex (previously called Reveal ctDNA), VariantPlex, FusionPlex, STRATAFIDE, Personalized Cancer Monitoring ("PCM"), and ArcherMET products, and any other oncology products that use the same technology as the previously mentioned products (collectively, the "Accused Products"). The Accused Products

all use Archer's Anchored Multiplex PCR ("AMP") on nucleic acids. Natera brings this action to stop Defendants' infringement of Natera's innovative, patented technology.

THE PARTIES

2. Plaintiff Natera is a corporation organized and existing under the laws of Delaware, with its principal place of business at 201 Industrial Road, San Carlos, California 94070.

3. Founded in 2004, Natera (f.k.a. Gene Security Network) is a pioneering molecular technology company with industry-leading healthcare diagnostics products. Natera is dedicated to improving disease management for oncology, reproductive health, and organ transplantation. For well over a decade, Natera has been researching and developing non-invasive methods for analyzing DNA in order to help patients and doctors manage diseases. These ongoing efforts have given rise to a number of novel and proprietary genetic testing services to assist with life- saving health management.

4. Since 2009, Natera has launched ten molecular tests, many of which are available through major health plans accounting for more than 140 million covered persons in the United States. Natera's own robust laboratory processes thousands of genetic tests per month.

5. Natera's pioneering and ongoing innovation is especially evident in the area of cell-free DNA ("cfDNA") based testing. In the cfDNA field, Natera has developed unique and highly optimized cfDNA-based processes that can be used to test non-invasively for a range of conditions. Natera developed an industry-leading cfDNA test, Panorama, which showcases Natera's mastery of cfDNA in the field of non-invasive diagnostics. Panorama is considered the industry leading test in this space, with over two million tests performed commercially and more than twenty-six peer-reviewed publications. Natera has also applied its cfDNA platform to the challenge of detecting and monitoring cancer.

6. In detecting and monitoring cancer, the use of minimally invasive, blood-based tests offers significant advantages over older more invasive methods, such as the tumor biopsy. But a significant technological challenge is that blood-based testing requires the measurement of very small amounts of relevant genetic material—circulating-tumor DNA ("ctDNA")—within a much larger blood sample. Natera's approach combines proprietary molecular biology and computational techniques to measure genomic variations in tiny amounts of DNA, representing a fundamental advance in molecular biology.

7. Natera has researched and developed cfDNA technology to provide patients and healthcare providers with tools for early clinically meaningful detection and monitoring of cancer.

8. Natera's cfDNA platform is the result of over a decade of hard work and investment of, on average, more than 50 million dollars per year in research and development. Natera has expended substantial resources researching and developing its technologies and establishing its reputation among physicians, insurers, and regulators as a company committed to sound science and consistently accurate, reliable results. This research, and the technological innovations resulting therefrom, are protected by a substantial patent portfolio, with over 200 patents issued or pending worldwide, including greater than 60 in the field of oncology.

9. Among these patented inventions is the '220 patent, which Archer infringes. Archer has used Natera's patented technology without permission and in violation of the patent laws.

10. ArcherDX, Inc. is a corporation organized and existing under the laws of the state of Delaware, having a principal place of business at 2477 55th Street, Suite 202, Boulder, CO 80301.

11. Defendant Invitae Corporation is a corporation organized and existing under the law of the state of Delaware, having a principal place of business at 1400 16th Street, San Francisco, California 94103.

12. Pursuant to Invitae's Form 8-K Report to the Securities and Exchange Commission, on October 2, 2020, Invitae consummated the acquisition of ArcherDX, Inc., with ArcherDX, LLC becoming a wholly-owned subsidiary of Invitae.

13. Defendant ArcherDX has represented that effective October 2, 2020, Defendant ArcherDX, Inc. merged with Apollo Merger Sub A Inc., which then merged with Apollo Merger Sub B LLC to form ArcherDX, LLC and that ArcherDX, LLC should be substituted for ArcherDX, Inc.

14. In the agreements related to the merger between Invitae and ArcherDX, Invitae represented to its shareholders that it will assume ArcherDX's risks from legal proceedings and that "[a]fter the completion of the merger, the surviving company [ArcherDX, LLC] and Invitae will control the lawsuit filed by Natera, Inc. against ArcherDX pursuant to the complaint filed in the United States District Court for the District of Delaware having the Case No. 1:20-CV-00125 or any other related case for infringement of any patent claim directly related to Case No. 1:20-CV-00125 (collectively, the "Natera Litigation")." Accordingly, Defendants ArcherDX, LLC and Invitae Corporation are successors-in-interest to ArcherDX, Inc. and have further continued to engage in the infringing conduct alleged in this Second Amended Complaint.

15. Instead of developing its own science for its cancer detection and monitoring products, Defendants have unlawfully used and are using Natera's patented technology.

JURISDICTION AND VENUE

16. This is an action for patent infringement arising under the patent laws of the United States, 35 U.S.C. § 1, *et seq*.

17. This Court has jurisdiction under 28 U.S.C. §§ 1331 and 1338(a) because this is a civil action arising under the Patent Act and declaratory judgment jurisdiction under 28 U.S.C. §§ 2201-2202.

18. This Court has personal jurisdiction over Archer because Archer is a Delaware corporation.

19. This Court also has jurisdiction over Archer because, upon information and belief, Archer, directly or indirectly, uses, offers for sale, and/or sells the Accused Products throughout the United States, including in this judicial district.

20. This Court also has jurisdiction over Archer because Archer has availed itself of this forum, initiating civil actions in this jurisdiction including *ArcherDX, Inc. et al v. QIAGEN Sciences, LLC et al*, C.A. 18-1019 MN (D. Del. 2018) and *Natera, Inc. v. ArcherDX, Inc.*, C.A. 20-0125 LPS (D. Del. 2020).

21. This Court has personal jurisdiction over Invitae because Invitae is a Delaware corporation and directly or indirectly, uses, offers for sale, and/or sells the Accused Products throughout the United States, including in this judicial district.

22. This Court has personal jurisdiction over Invitae and Archer because they are successors-in-interest to ArcherDX, Inc.

23. This Court also has jurisdiction over Invitae because, upon information and belief, Invitae is vicariously liable for the infringing acts of Archer in that Invitae has directed or authorized the infringing activities of Archer since the October 2 merger. In the alternative, Invitae

is the alter ego of Archer, where a unity of interest and ownership exists between Invitae and Archer such that separate personalities of the two do not in reality in exist. In the agreements related to the merger between Invitae and ArcherDX, Inc., Invitae represented to its shareholders that it will assume ArcherDX, Inc.'s risks from legal proceedings and that "[a]fter the completion of the merger, the surviving company [ArcherDX, LLC] ***and Invitae will control the lawsuit*** filed by Natera, Inc. against ArcherDX pursuant to the complaint filed in the United States District Court for the District of Delaware having the Case No. 1:20-CV-00125 or any other related case for infringement of any patent claim directly related to Case No. 1:20-CV-00125 (collectively, the "Natera Litigation")."

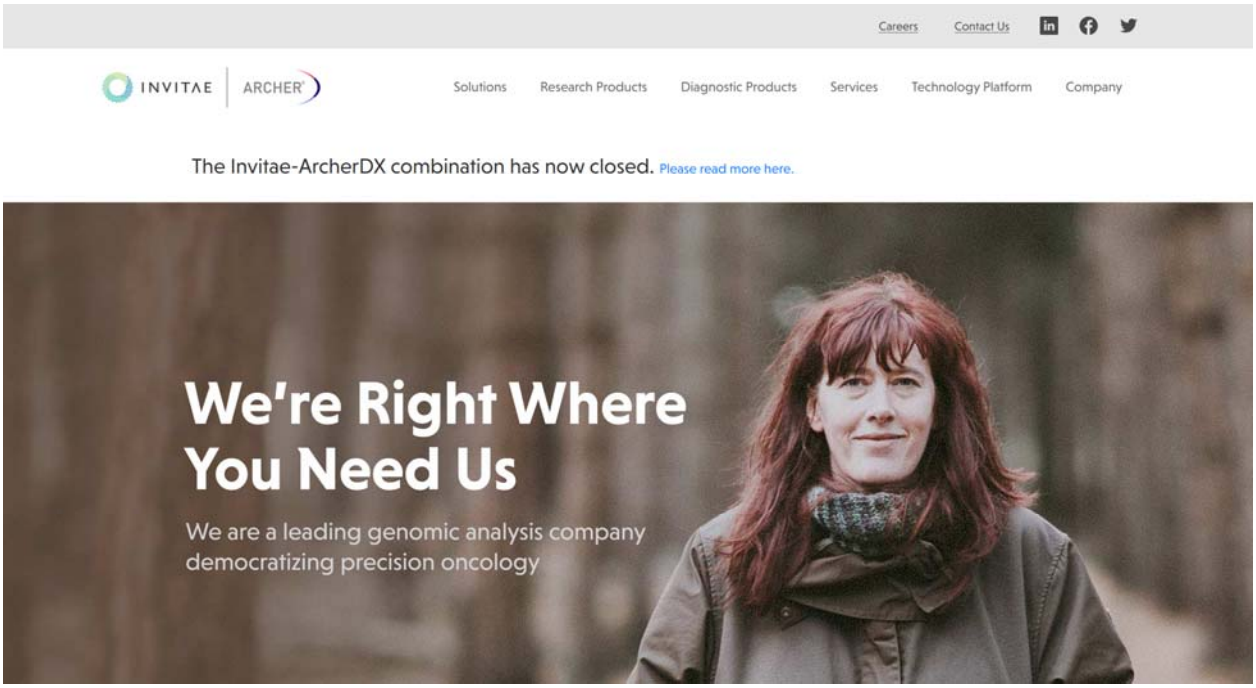
24. The Invitae's Board of Directors represented that Invitae and ArcherDX, LLC were to be united through the merger. Specifically, the Invitae Board represented:

> A belief that ***uniting*** Invitae and ArcherDX would accelerate the ability ***of the combined company*** to offer comprehensive support for precision oncology, including due to the potential represented by the combination of (i) Invitae's platform, including leadership in diagnostic and hereditary risk testing and strong relationships with clinicians caring for cancer patients, including cancer genetic counselors, oncologists and imaging centers, and (ii) ArcherDX's platform, with its proprietary Anchored Multiplex PCR (AMPTM) chemistry at the core, which has enabled ArcherDX to develop products and services under investigation to optimize therapy and enable cancer monitoring across liquid and tissue samples.

25. The prospectus for the merger represented: "The merger involves the ***integration*** of two companies that have previously operated independently. Prior to announcement, Invitae and ArcherDX did not conduct any integration planning for the two companies, and their ability to do so prior to consummation of the merger may be substantially limited by applicable law. After the merger, the two companies ***will devote significant management attention and resources to integrating the two companies***."

26. Invitae's 10-02-2020 Form 8-K represented to the investing public: "Invitae Corporation (NYSE: NVTA), a leading genetics company, today announced that on October 2, 2020, it completed the transaction ***to bring ArcherDX, a leading genomics analysis company, into Invitae*** to create a comprehensive offering that provides testing services for disease risk, therapy optimization and personalized cancer monitoring to enable precision approaches to cancer treatment. 'With the addition of ArcherDX's technologies, capabilities and team, Invitae is now well positioned to accelerate the utilization of genetic information throughout a cancer patient's journey. Starting from risk profiling and diagnostic testing, moving to therapy optimization, monitoring and recurrence surveillance, Invitae can deliver the information needed to enable best-in-class personalized cancer care,' said Sean George, Ph.D., co-founder and chief executive officer of Invitae. 'Invitae is on a mission to increase access to molecular medicine to all who can benefit, and the addition of the ArcherDX platform builds out an important segment serving the current and future oncology landscape.'"

27. Archer's website displays the names and logos of both Invitae and Archer, proclaims "The Invitae-ArcherDX combination has now closed" and "We're Right Where You Need Us" underscoring the unity of Archer and Invitae. *See* https://archerdx.com/



28. Invitae announced the FDA's acceptance of its Premarket approval application for the accused product, Stratafide. "***Invitae*** on Monday ***said that the US Food and Drug Administration has accepted a premarket approval application for the Stratafide*** next-generation sequencing companion diagnostic. ***Invitae acquired the test*** after it bought ArcherDx last month for $1.4 billion." (Ex. 42, Nov. 23, 2020 announcement, "FDA accepts ***Invitae Premarket Approval Submission*** for Stratafide Companion Diagnostic" at https://www.genomeweb.com/regulatory-news-fda-approvals/fda-accepts-invitae-premarket-approval-submission-stratafide-companion#:~:text=NEW%20YORK%20%E2%80%93%20Invitae%20on%20Monday,last%20month%20for%20%241.4%20billion) (emphasis added).

29. Finally, on information and belief, upon the merger's closing, the former CEO for ArcherDx was named to the Invitae Board and serves as the president of Invitae's oncology division.

30. Venue is proper in this Court under 28 U.S.C. § 1400(b) because Archer is a Delaware corporation.

31. Venue is proper in this Court under 28 U.S.C. § 1400(b) because Invitae is a Delaware corporation.

BACKGROUND

32. Since 2004, Natera has been a global leader in genetic testing, diagnostics, and DNA testing, including cfDNA testing. Natera's mission is to improve the management of disease worldwide and focuses on reproductive health, oncology, and organ transplantation. In pursuit of these goals, Natera has developed novel technologies to make significant and accurate clinical assessments from the miniscule amounts of cfDNA present in a single blood sample. These technologies include methods to manipulate cfDNA in unconventional ways in order to capture information about genetic variations in cfDNA and usefully transform that information for noninvasive testing.

33. Natera develops and commercializes innovative, non-traditional methods for manipulating and analyzing cfDNA, and offers a host of proprietary cfDNA genetic testing services to the public to assist patients and doctors to evaluate and track critical health concerns.

34. Since its founding, Natera has researched, developed, and released ten molecular tests with applications in prenatal diagnostics, cancer, and organ transplants, many of which are available through major health plans, or covered by Medicare or Medicaid, and therefore available to most patients in need of those tests. Natera's tests have helped more than two million people to date. Natera's robust laboratory now processes tens of thousands of tests per month in the United States and internationally, improving the ability of physicians to monitor and manage crucial health issues and patients to prosper around the world.

35. Building on these innovations, in 2017, Natera launched its cfDNA diagnostic test to detect and monitor cancer, called Signatera®. Signatera® is a personalized ctDNA surveillance tool that detects minimal residue disease ("MRD") when assessing disease recurrence or treatment response in solid tumors. Signatera® is designed to screen for multiple tumor-derived targets with each assay. It is optimized to detect extremely low quantities of ctDNA and provides early knowledge of disease recurrence with a >99.5% clinical test specificity.

36. MRD assessment has become a standard of care in the management of patients with hematological malignancies, but until recently it has not been possible in solid cancers due to technical limitations. Accurate MRD testing and molecular monitoring offers the potential for physicians to change or escalate treatment in patients who are MRD-positive, and to de-escalate or avoid unnecessary treatment in patients who are MRD-negative. It also holds potential as a surrogate endpoint in clinical trials.

37. Natera's technology has been validated in multiple clinical studies. In Cancer Research UK/University College London's Tracking Cancer Evolution through Therapy ("TRACERx"), Natera's technology was used for the multi-year monitoring of patient-specific single-nucleotide variants (SNVs) in plasma, to understand the evolution of cancer mutations over time, and to monitor patients for disease recurrence. Results from the first 100 early-stage lung cancer patients analyzed as part of the study were featured on the cover of the May 2017 issue of Nature and showed that an early prototype version of Signatera® identified 43% more ctDNA-positive early-stage lung cancer cases than a generic lung cancer panel and demonstrated its potential to detect residual disease, measure treatment response, and identify recurrence up to 11 months earlier than the standard of care, with a sensitivity of 93% at time of relapse.

38. Natera has also collaborated with Aarhus University in Denmark, Imperial College London, University of Leicester, Institute Jules Bordet, Fox Chase Cancer Center, University of California, San Francisco, and Foundation Medicine, Inc. with respect to cancer research.

39. The U.S. Food and Drug Administration ("FDA") recognized the importance of Natera's Signatera® and granted it "Breakthrough Device" designation on May 6, 2019. That designation will help accelerate FDA assessment and review of Signatera® as an *in vitro* diagnostic.

40. Signatera®'s validation has also led Medicare to issue a draft Local Coverage Determination ("LCD") for Signatera® in March 2019. In its draft LCD, Medicare determined that "[t]he analytical validity and clinical validity of minimal residual disease testing using cell-free DNA, and Signatera® in particular, appears to be well established based on available information for the test." In August 2019, the Palmetto MolDX program, which is run by Medicare Administrative Contractors, proposed a LCD for use of the "Signatera molecular residual disease (MRD) test in patients with certain forms of colorectal cancer."

41. The '220 patent resulted from Natera's years-long research in developing innovative new methods for amplifying and sequencing nucleic acids, including cell-free DNA.

General Background of the Invention

42. The '814 patent, attached hereto as Exhibit 1, is entitled "Methods for Simultaneous Amplification of Target Loci" and was issued by the United States Patent and Trademark Office ("USPTO") on January 21, 2020. Natera owns the '814 patent, including the right to enforce it and seek damages for infringement.

43. The '814 patent claims methods for simultaneously amplifying multiple nucleic acid regions of interest in a single reaction volume. The claimed methods use polymerase chain

reaction ("PCR") to amplify and high-throughput sequencing ("HTS") to sequence the nucleic acids. Independent claim 1 of the '814 patent recites:

> A method for amplifying and sequencing DNA, comprising:
>
> ligating adaptors to cell-free DNA isolated from a biological sample, wherein the adaptors each comprises a universal priming site;
>
> performing a first PCR to simultaneously amplify at least 10 target loci using a universal primer and at least 10 target-specific primers in a single reaction volume;
>
> performing a second, nested PCR to simultaneously amplify the at least 10 target loci using the universal primer and at least 10 inner target-specific primers in a single reaction volume, wherein at least one of the primers comprises a sequencing tag;
>
> performing high-throughput sequencing to sequence the amplified DNA comprising the target loci.

44. The '172 patent, attached hereto as Exhibit 2, is entitled "Methods for Simultaneous Amplification of Target Loci" and was issued by the United States Patent and Trademark Office ("USPTO") on February 11, 2020. Natera owns the '172 patent, including the right to enforce it and seek damages for infringement.

45. The '172 patent claims methods for simultaneously amplifying multiple nucleic acid regions of interest in a single reaction volume. The claimed methods use polymerase chain reaction ("PCR") to amplify and high-throughput sequencing ("HTS") to sequence the nucleic acids. Independent claim 1 of the '172 patent recites:

> A method for amplifying and sequencing DNA, comprising:
>
> isolating cell-free DNA from a biological sample and tagging the isolated cell-free DNA, wherein each tagged DNA molecule comprises a molecular barcode;
>
> performing a first PCR to simultaneously amplify at least 10 target loci using a universal primer and at least 10 target-specific primers in a single reaction volume;
>
> performing a second, nested PCR to simultaneously amplify the at least 10 target loci using the universal primer and at least 10 inner target-specific primers in a single reaction volume;
>
> performing high-throughput sequencing to sequence the amplified DNA comprising the target loci.

46. The '482 patent, attached hereto as Exhibit 3, is entitled "Amplification of cell-free DNA using nested PCR" and was issued by the United States Patent and Trademark Office ("USPTO") on March 17, 2020. Natera owns the '482 patent, including the right to enforce it and seek damages for infringement.

47. The '482 patent claims methods for simultaneous nested amplification of multiple nucleic acid regions of interest in a single reaction volume. Independent claim 1 of the '482 patent recites:

> A method for nested PCR amplification, comprising:
>
> isolating cell-free DNA from a biological sample and ligating adaptors to the isolated cell-free DNA, wherein the adaptors each comprise a universal priming site, wherein (i) the adaptors each comprise a molecular barcode and/or (ii) at least one of the primers comprises a sequencing tag;
>
> performing a first PCR to simultaneously amplify at least 10 target loci using a universal primer and at least 10 target-specific primers in a first reaction volume; and
>
> performing a second, nested PCR to simultaneously amplify the at least 10 target loci using the universal primer and at least 10 inner target-specific primers in a second reaction volume to obtain amplified DNA, wherein primer binding sites of the inner target specific primers of the second PCR are internal to primer binding sites of the target-specific primers of the first PCR, wherein at least 80% of the amplified DNA maps to the target loci.

48. The '708 patent, attached hereto as Exhibit 4, is entitled "Methods for Simultaneous Amplifications of Target Loci" and was issued by the United States Patent and Trademark Office ("USPTO") on March 24, 2020. Natera owns the '708 patent, including the right to enforce it and seek damages for infringement.

49. The '708 patent claims methods for simultaneously amplifying multiple nucleic acid regions of interest in a reaction mixture. The claimed methods amplify the nucleic acids under particular reaction conditions and sequence the nucleic acids. Independent claim 1 of the '708 patent recites:

> A method of amplifying target loci in a nucleic acid sample, the method comprising:
>
> contacting the nucleic acid sample comprising target loci with a library of at least 2 primers that simultaneously hybridize to at least 2 of the target loci to produce a reaction mixture;
>
> subjecting the reaction mixture to primer extension reaction conditions to produce amplified products comprising target amplicons; wherein the annealing temperature for the reaction conditions is greater than a melting temperature of the at least 2 primers, wherein the length of the annealing step of the reaction conditions is greater than 3 minutes, and wherein the at least 2 of the target loci are simultaneously amplified; and sequencing the amplified products.

50. The '220 patent, attached hereto as Exhibit 5, is entitled "Methods for Simultaneous Amplification of Target Loci" and was issued by the United States Patent and Trademark Office ("USPTO") on August 4, 2020.

51. Natera is the owner of all rights, title, and interest to the '220 patent which is valid and enforceable.

52. The '220 patent issued from Application No. 16/743,724, filed on January 15, 2020. Application No. 16/743,724 is a continuation of Application No. 14/918,544, filed on October 20, 2015.

53. The '220 patent shares the specification of Application No. 14/918,544, filed on October 20, 2015.

54. On or before October 20, 2015, no employee of Archer had worked at Natera.

55. The '220 patent claims methods for simultaneously amplifying multiple nucleic acid regions of interest in a single reaction volume using universal primers, gene specific primers and molecular barcode. The claimed methods recite ligating adaptors to cell-free DNA followed by two polymerase chain reactions ("PCR") to amplify and high-throughput sequencing ("HTS") to sequence the newly created nucleic acids. Independent claim 1 of the '220 patent recites:

> A method for amplifying and sequencing DNA, comprising:

> ligating adaptors to cell-free DNA isolated from a biological sample, wherein the adaptors each comprises a universal priming sequence and a molecular barcode;
>
> performing a first PCR to simultaneously amplify at least 10 target loci using a first universal primer and at least 10 target-specific primers in a single reaction volume;
>
> performing a second, nested PCR to simultaneously amplify the at least 10 target loci using a second universal primer and at least 10 inner target-specific primers in a single reaction volume, wherein at least one of the primers comprises a sequencing tag; and
>
> performing high-throughput sequencing to sequence the amplified DNA comprising the target loci.

The '814 Patent Is Not Directed to a Natural Phenomenon and Its Steps Were Not Routine or Conventional

56. The claims of the '814 patent are not directed to a natural law or natural phenomenon. Rather, they are directed to amplifying and sequencing DNA in a sample using synthetic primers and amplification products to provide a novel and innovative solution to problems peculiar to the particular problem of amplifying and sequencing small amounts of cell-free DNA from tumor cells in a biological sample. Moreover, the claims of the '814 patent cover methods of preparation. Analogous claims were held not be directed to a natural law or phenomenon in the recent Federal Circuit decision in *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, No. 2019-1419, 2020 WL 1264002 (Fed. Cir. Mar. 17, 2020).

57. The '814 patent claims are directed to specific, unconventional, non-routine methods for overcoming previously unresolved problems in this area. For example, as of the date of the invention, it would not have been routine or conventional to amplify and use HTS to sequence nucleic acids obtained from circulating tumor DNA with the use of a universal primer and a sequencing tag in the context of the invention.

58. In allowing '814 patent claims, the USPTO examiner found the claims to be non-routine and non-conventional, and stated:

> [T]he claims have been carefully reviewed and the claimed invention distinguishes over the art because the closest references in the art do not teach, or render obvious, each aspect of the claimed invention. The closest art, Chowdary et al. (US PgPub 20080305473; December 2008) teaches a method of nested multiplex amplification of circulating tumor cells, but there are significant differences between the teachings of Chowdary and the claimed method steps. Chowdary focuses on amplification of nucleic acids obtained from circulating tumor cells and not on circulating nucleic acids, Chowdary does not teach any sequencing steps, does not incorporate a universal or common primer and does not include a sequencing tag. Further, Chowdary specifically teaches away from modification to focus on circulating nucleic acids, Chowdary specifically includes a step of isolation of circulating tumor cells (CTCs) followed by extraction of nucleic acids and amplification of the nucleic acid, steps which would exclude modifying Chowdary to arrive at the method steps as claimed.
>
> Further, an additional reference, Gocke et al. (US Patent 6156504; December 2000) teaches analysis of circulating nucleic acids that include semi-nested amplification, and a general mention of multiplex amplification. However, there are also significant differences between Gocke and the claimed method steps because Gocke only mentions sequencing in a prophetic example, does not teach or suggest the inclusion of universal or common primers or the inclusion of sequencing tags.
>
> Therefore, since neither Chowdary nor Gocke teach or suggest each and every step of the method, as claimed, the claims are novel and non-obvious over the prior art.

59. None of the references U.S. Patent App. Pub. No. 2010/0120038 ("Mir"), Diego Spertini, *Screening of Transgenic Plants by Amplification of Unknown Genomic DNA Flanking T-DNA*, 27 BioTechniques 308 (1999) ("Spertini"), and U.S. Patent App. No. 2007/0031857 ("Makarov"), either alone or in combination with each other, anticipate or render obvious any of the claims of the '814 patent.

The '172 Patent Is Not Directed to a Natural Phenomenon and Its Steps Were Not Routine or Conventional

60. The claims of the '172 patent are not directed to a natural law or natural phenomenon. Rather, they are directed to amplifying and sequencing DNA in a sample using synthetic primers and amplification products to provide a novel and innovative solution to problems peculiar to the particular problem of amplifying and sequencing small amounts of cell-free DNA from tumor cells in a biological sample. Moreover, the claims of the '172 patent cover

methods of preparation. Analogous claims were held not be directed to a natural law or phenomenon in the recent Federal Circuit decision in *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, No. 2019-1419, 2020 WL 1264002 (Fed. Cir. Mar. 17, 2020).

61. The '172 patent claims are directed to specific, unconventional, non-routine methods for overcoming previously unresolved problems in this area. For example, as of the date of the invention, it would not have been routine or conventional to amplify and use HTS to sequence nucleic acids obtained from cell-free DNA with the use of a universal primer and a molecular barcode in the context of the invention.

62. In allowing '172 patent claims, the USPTO examiner found the claims to be non-routine and non-conventional, and stated:

> [T]he claims have been carefully searched and the claimed invention distinguishes over the art. The closest references in the art do not teach, or render obvious, each aspect of the claimed invention. The closest art, Chowdary et al. (US PgPub 20080305473; December 2008) teaches a method of nested multiplex amplification, of circulating tumor cells. However, there are significant differences between the teachings of Chowdary and the claimed invention, as Chowdary focuses on amplification of nucleic acids obtained from circulating tumor cells and not on circulating nucleic acids, Chowdary does not teaching sequencing steps and does not incorporate a universal or otherwise common primer within the amplification. Further, Chowdary specifically teaches away from modification to analyze circulating nucleic acids, as the method includes specific isolation of circulating tumor cells (CTCs) followed by extraction of nucleic acids and amplification of the nucleic acid.
>
> Further, an additional reference, Gocke et al. (US Patent 6156504; December 2000) teaches analysis of circulating nucleic acids that include semi-nested amplification, and a general mention of multiplex amplification. However, there are also significant differences between Gocke and the claimed method, as Gocke only mentions sequencing in a prophetic example, and does not teach or suggest either universal or common primers for the amplification steps.
>
> Therefore, as both Chowdary and Gocke do not teach or suggest each and every step of the method, as claimed, the claims are novel and non-obvious over the prior art.

The '482 Patent Is Not Directed to a Natural Phenomenon and Its Steps Were Not Routine or Conventional

63. The claims of the '482 patent are not directed to a natural law or natural phenomenon. Rather, they are directed to amplifying DNA in a sample using synthetic primers and amplification products to provide a novel and innovative solution to problems peculiar to the particular problem of amplifying small amounts of cell-free DNA from tumor cells in a biological sample. Moreover, the claims of the '482 patent cover methods of preparation. Analogous claims were held not be directed to a natural law or phenomenon in the recent Federal Circuit decision in *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, No. 2019-1419, 2020 WL 1264002 (Fed. Cir. Mar. 17, 2020).

64. The '482 patent claims are directed to specific, unconventional, non-routine methods for overcoming previously unresolved problems in this area. For example, as of the date of the invention, it would not have been routine or conventional to use nested PCR amplification to amplify nucleic acids obtained from circulating tumor DNA with the use of a universal primer, and wherein at least 80% of the amplified DNA maps to the target loci, in the context of the invention.

65. In allowing '482 patent claims, the USPTO examiner found the claims to be non-routine and non-conventional, and stated:

> The claims are free of the analogous art at least because the art does not teach the recited 'nested PCR' following the recited 'first PCR' of 'cell-free DNA' with the recited amplification targeting.

The '708 Patent Is Not Directed to a Natural Phenomenon and Its Steps Were Not Routine or Conventional

66. The claims of the '708 patent are not directed to a natural law or natural phenomenon. Rather, they are directed to amplifying and sequencing nucleic acid samples using synthetic primers and amplification products to provide a novel and innovative solution to

problems peculiar to the particular problem of amplifying and sequencing small amounts of nucleic acid samples. Moreover, the claims of the '708 patent cover methods of preparation. Analogous claims were held not be directed to a natural law or phenomenon in the recent Federal Circuit decision in *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, No. 2019-1419, 2020 WL 1264002 (Fed. Cir. Mar. 17, 2020).

67. The '708 patent claims are directed to specific, unconventional, non-routine methods for overcoming previously unresolved problems in this area. For example, as of the date of the invention, it would not have been routine or conventional to amplify and sequence nucleic acids obtained from nucleic acid samples with the use of multiple primers that simultaneously hybridize, and wherein the melting temperature of at least two of the pairs of primers is less than the annealing temperature used, in the context of the invention.

68. In allowing '708 patent claims, the USPTO examiner found the claims to be non-routine and non-conventional, and stated:

> Applicant's arguments regarding Spier and Ishii are persuasive regarding the claimed feature of selecting an annealing temperature greater than the melting temperature of at least two of the pairs of primers. Further, Applicant's arguments regarding the significant advantages provided by the selection of the higher annealing temperature in reduction of primer dimer formation were particularly persuasive as evidence of the non-obviousness of the claimed invention.
>
> The prior art does not teach or suggest each of the features of the claimed method including the selection of an annealing temperature higher than the melting temperature of the primers, the selection of a long annealing time and sequencing of the amplification products. Therefore the claims are novel and nonobvious over the prior art.

The '220 patent Is Not Directed to a Natural Phenomenon and Its Steps Were Not Routine or Conventional

69. The claims of the '220 patent are a patentable and innovative solution to a significant problem in using cell-free DNA that specifically addresses the difficulty in simultaneously amplifying multiple DNA targets and sequencing them. The claims are directed

to an improved process for preparing non-natural DNA, and are analogous to claims found patentable in *Illumina, Inc. v. Ariosa Diagnostics, Inc.*, 967 F.3d 1319 (Fed. Cir. Aug. 3, 2020).

70. At the time of the invention, skilled artisans were interested in "simultaneous amplification of many target nucleic acids in a sample of interest" (called "multiplex PCR") because such a process could "significantly simplify experimental procedures and shorten the time required for nucleic acid analysis and detection." '220 Patent, 2:62-3:3. Such amplification involved the use of man-made DNA molecules called "primers" that bind to certain DNA regions. But there was a problem doing this:

> **[W]hen multiple pairs [of primers] are added to the same PCR reaction, non-target amplification products may be generated, such as amplified primer dimers**. The risk of generating such products increases as the number of primers increases. These non-target amplicons significantly limit the use of amplified products for further analysis and/or assays.

'220 Patent, 3:4-9 (emphasis added). In essence, the primers bind to and amplify themselves rather than their intended targets. These amplified primer-dimer artifacts then compete with the actual amplified targets at the sequencing stage, resulting in significant problems. '220 Patent, 47:36-44, 86:11-14. One solution, the patent explains, was to split up the reactions into individual PCR reactions with a single primer pair or a smaller number of primer pairs. '220 Patent, 86:18-21. But if there is only a small amount of sample DNA to start with (as is often the case when analyzing cell-free DNA), dividing that limited amount into even smaller reaction vessels is impractical. '220 patent, 86:21-25. Thus, Natera's patent explains, "improved methods are needed to reduce the formation of non-target amplicons during multiplex PCR." '220 Patent, 3:9-11.

71. The patent teaches and claims a solution to this problem—a method for ***preparing a non-natural*** DNA and sequencing it. The method includes specific process steps. First, cell-free DNA is altered by ligating a man-made adaptor to it, thereby creating an artificial DNA. Once ligated, these adapters are ***never removed***. The next claimed step leads to an even more

unnatural result where some—but not all—of the adapter-bearing molecules are selectively amplified using human engineered "target specific" primers and the previously added universal primer. The end result of this step is a mixture having unnaturally enriched copies of certain DNA sequences. These copies are enriched further in the next claimed step, and also receive a new artificial addition—a sequencing tag. Finally, the enriched fraction of these artificial DNA copies is sequenced using a high-throughput approach. As such, the claims are not directed to the detection of the cell-free DNA itself or directed to a natural law or natural phenomenon.

72. The '220 Patent claims are directed to specific, unconventional, non-routine, improved methods for overcoming the previously unresolved problems in this area. For example, as of the date of the invention, it would not have been routine or conventional to amplify and use high-throughput sequencing to sequence nucleic acids obtained from circulating tumor DNA with the use of universal primers, molecular barcode and a sequencing tag in the context of the invention. The patent specification explains that sequencing was problematic after multiplex PCR because of artifacts such as primer-dimers formed during the amplification process, skilled artisans were therefore using methods such as microarrays instead of sequencing, and now that the patent teaches a way to minimize the formation of primer-dimer artifacts, multiplex PCR followed by sequencing could be done more effectively. '220 Patent, 47:36-55.

73. In allowing the '220 Patent claims, the USPTO examiner found the claims to be non-routine and non-conventional, and stated:

> Claims 24-26 are free of the art. There are references that teach aspects of the method but would not render the claims obvious over these references because there is no motivation to modify a reference like Chowdary et al. (US PgPub 20080305473; December 2008) or Gocke et al (US Patent 6,156,504; December 2000) to include both multiplex using universal or common primers and a second step of nested amplification on the same multiplex amplified targets.

(Ex. 11, March 6, 2020 Non-final rejection, at p.5.)

74. None of the references U.S. Patent App. Pub. No. 2010/0120038 ("Mir"), Diego Spertini, *Screening of Transgenic Plants by Amplification of Unknown Genome DNA Flanking T-DNA*, 27 BioTechniques 308 (1999) ("Spertini"), and U.S. Patent App. No. 2007/0031857 ("Makarov"), either alone or in combination with each other, anticipate or render obvious any of the claims of the '220 Patent.

DEFENDANTS' INFRINGING ACTIVITIES

75. On information and belief, Defendants and/or its end-users perform every step of claim 1 of the Asserted Patents when they use any of the Accused Products. Defendants' website with both Invitae's and Archer's names and logos states: "At the core of every Archer® panel is our AMP chemistry developed to create target-enriched libraries for next-generation sequencing (NGS)" and "AMP chemistry is also flexible, so it can be used for applications in DNA, RNA, and ctDNA sequencing across most tumor types." (Ex. 12, https://archerdx.com/technology-platform/technology/.)

76. "Archer admits that it operates a CLIA-certified laboratory." Archer's Answer, *Natera, Inc. ArcherDX, Inc.,* Case No. 20-125-LPS, D.I 21 at ¶ 110. On information and belief, Defendants perform every step of claim 1 of the Asserted Patents when using the Accused Products in the laboratory and sequencing the amplified DNA.

77. On information and belief, Defendants also sell the Accused Products to its customers, including research organizations and pharmaceutical companies (collectively "end-users") who use the accused products by performing every step of claim 1 of the Asserted Patents.

78. Archer avers that its products, "including custom kits, are sold as 'research use only' products to customers, including researchers, clinical laboratories, contract research organizations, and pharmaceutical and biotechnology companies (collectively, "End-users")."

Archer's Amended Complaint, *ArcherDX, Inc. v. Qiagen Science, LLC*, Case No. 18-1019 MN (D. Del.), D.I. 130, at ¶ 20.

79. Archer further avers that its "products may be used in research and laboratory developed tests ("LDT") for the detection of genes involved in cancer, and Archer sells standardized kits directed to certain disease segments. . . . In addition to its standardized kits encompassing AMP™ technology, Archer also sells custom kits specifically designed to meet the needs of a particular customer. For example, Archer® VariantPlex® kits for inherited diseases are highly customizable assays that deliver comprehensive coverage of target exons for genes associated with breast cancer risk (BRCA 1/2 & PALB2), cystic fibrosis (CFTR), and many other indications a customer may request." Archer's Amended Complaint, *ArcherDX, Inc. v. Qiagen Science, LLC*, Case No. 18-1019 MN, D.I. 130, at ¶ 20.

80. Attached as Exhibits 6-10 are preliminary and exemplary claim charts describing Archer's infringement of claim 1 of the Asserted Patents. Exhibits 12-41 are supporting documents for the Exhibits 6-10 charts. The claim charts are not intended to limit Natera's right to modify the chart or allege that other activities of Defendants infringe the identified claim or any other claims of the Asserted Patents or any other patents. Archer infringes more than one claim of the Asserted Patents.

81. Exhibits 6-10 are hereby incorporated by reference in its entirety. Each claim element in Exhibits 6-10 that is mapped to the Accused Products, and any other oncology products that use the same technology as the previously mentioned products shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each claim element is required.

82. On information and belief, Defendants and/or its end-users perform the AMP™ technology process to amplify DNA when using the Accused Products. AMP stands for "Anchored Multiplex PCR." Archer admits that its AMP™ technology is utilized to "preferentially enrich highly fragmented ctDNA [and] DNA." Archer's Answer, *Natera, Inc. ArcherDX, Inc.*, Case No. 20-125-LPS, D.I. 21, ¶ 48.

83. On information and belief, Defendants and/or its end-users sequence DNA created by using any of the Accused Products. Archer states that its AMP™ technology is used "create target-enriched libraries for next-generation sequencing (NGS)." (Ex. 12, https://archerdx.com/technology-platform/technology/.) Both Invitae's and Archer's names and logos are displayed in this webpage.

84. Below is "[t]he workflow of anchored multiplex PCR with molecular barcoding technology (MBC)" in Archer Reveal ctDNA product, which is now called LiquidPlex. (Ex. 13, Cheng, et al., "Clinical Validation of a Cell-Free DNA Gene Panel," J Mol Diagn, Vol. 21, Issue 4, Pages 632-64, at 634 (July 2019) (emphasis added).)

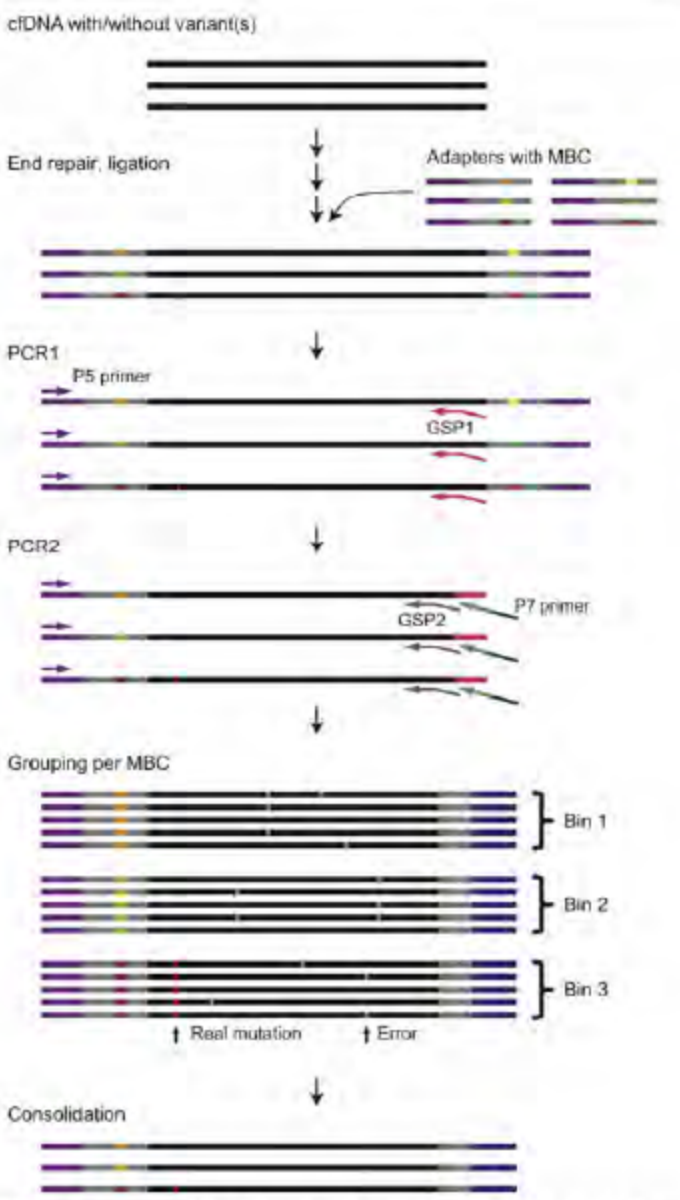
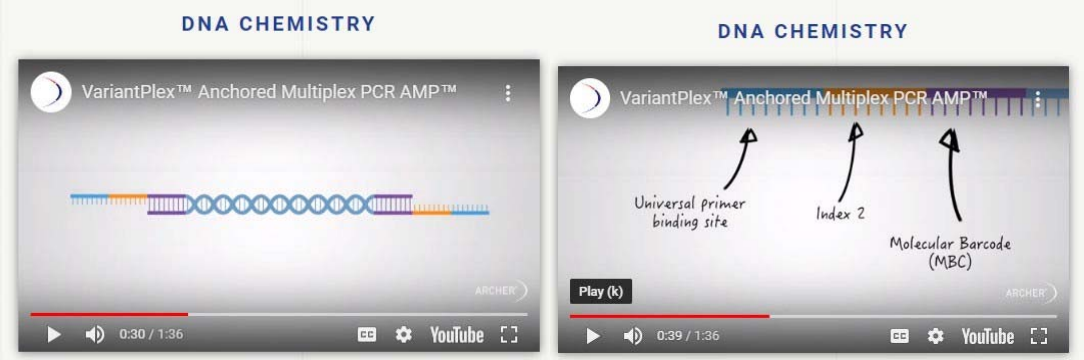


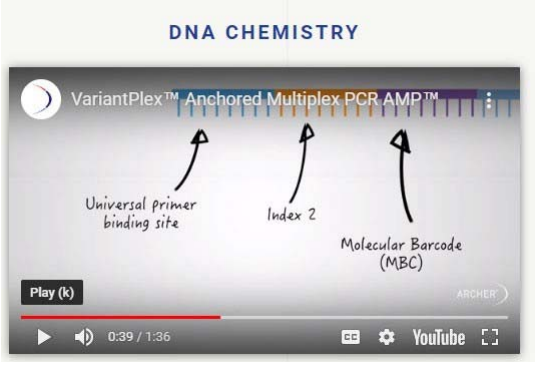
Figure 1 The workflow of anchored multiplex PCR with molecular barcoding technology (MBC). Cell-free DNA (cfDNA) fragments are end repaired and ligated to adapters with MBC (random 8-mer in different colors) and then amplified with two rounds of PCR using P5 primer and gene-specific primers (GSPs). After PCR and cleanup, the libraries are ready for quantitation and sequencing. Sequencing reads derived from the same template are grouped into the same bin, according to the sequence of MBC.

85. On information and belief, Defendants and/or its end-users ligate adaptors to cell-free DNA when using the Accused Products. Archer states that its AMP technology includes "**ligating an adapter molecule to the starting cDNA or DNA fragments** prior to PCR amplification." (Ex. 14, Archer Technical Note, "The use of molecular barcodes in anchored

multiplex PCR, at p. 1 (emphasis added).) In its website, Archer includes a video of AMP™ technology that shows that "adaptors are [] ligated on both ends" of the DNA. (Ex. 12, https://archerdx.com/technology-platform/technology/.) Both Invitae's and Archer's names and logos are displayed in this webpage.

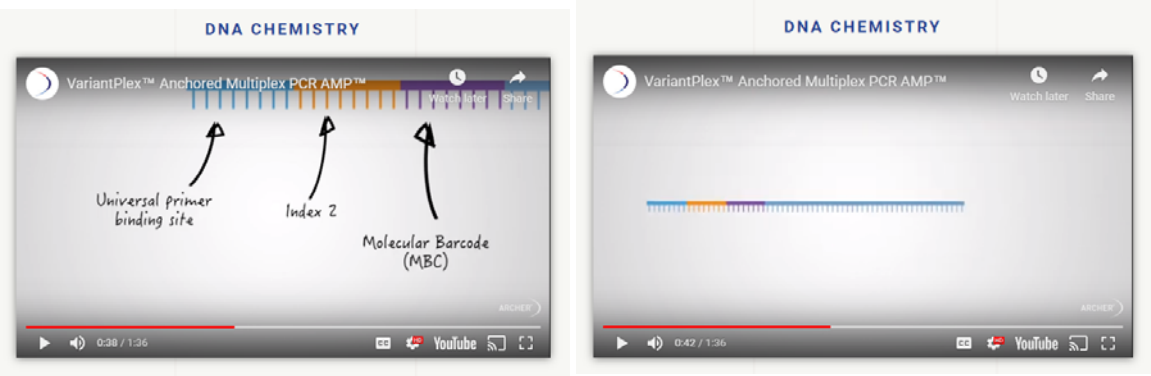


86. On information and belief, Defendants and/or its end-users use adaptors that include a universal priming sequence and a molecular barcode when using the Accused Products. In its website, Archer includes a video of AMP™ technology that shows that the adaptors it uses include a "universal primer binding site" and a "molecular barcode (MBC)." (Ex. 12, https://archerdx.com/technology-platform/technology/.) Both Invitae's and Archer's names and logos are displayed in this webpage.



87. On information and belief, Defendants use 1024 or more molecular barcodes when using the Accused Products. The video of AMP™ technology in Archer's website shows a

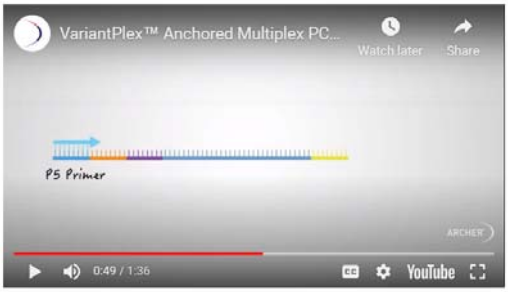
molecular barcode with 8 nucleotides. (Ex. 12, https://archerdx.com/technology-platform/technology/.) Both Invitae's and Archer's names and logos are displayed in this webpage.

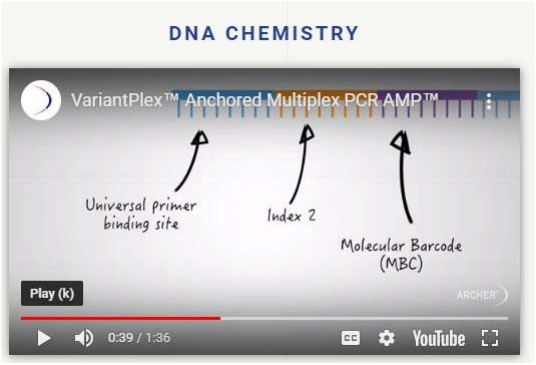


88. Archer has stated that it uses "a random 8-mer molecular barcode." (Ex. 14, Archer Technical Note, "The use of molecular barcodes in anchored multiplex PCR, at p. 1 (emphasis added).) The total number of different barcodes can be computed using 4^n, where n is the number of nucleotides. Given that the molecular barcode in AMP™ technology has 8 nucleotides, 65636 different barcodes are available.

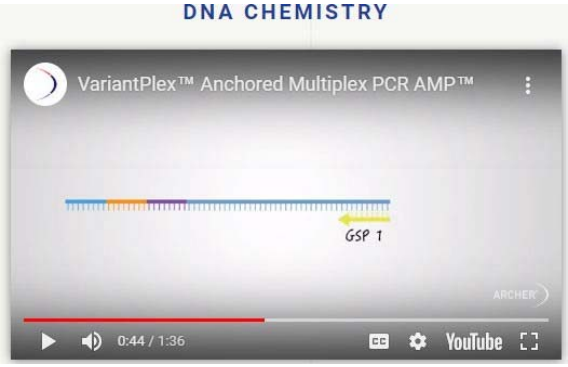
89. On information and belief, Defendants and/or its end-users then perform a PCR reaction when using the Accused Products. Archer states that its AMP technology includes "ligating an adapter molecule to the starting cDNA or DNA fragments prior to **PCR amplification**." (Ex. 14, Archer Technical Note, "The use of molecular barcodes in anchored multiplex PCR, at p. 1 (emphasis added).)

90. On information and belief, Defendants and/or its end-users perform the first PCR reaction using a universal primer when using the Accused Products. In the video of AMP™ technology in its website, Archer states that AMP™ technology uses P5 primer and the P5 primer includes a "universal primer binding site." (Ex. 12, https://archerdx.com/technology-platform/technology/.) Both Invitae's and Archer's names and logos are displayed in this webpage.

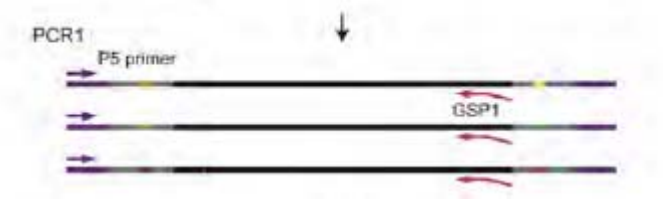




91. On information and belief, Defendants and/or its end-users perform the first PCR reaction using at least 10 gene-specific primers (GSP1) to amplify at least 10 targets when using the Accused Products. The video on Archer's AMP webpage states that "the first PCR uses an anchored gene specific primer [GSP1] . . ." (Ex. 12, https://archerdx.com/technology-platform/technology/.) Both Invitae's and Archer's names and logos are displayed in this webpage.



92. Cheng et al, who used the Archer Reveal ctDNA 28 kit (now called LiquidPlex), describe the steps they performed as follows: "Cell-free DNA . . . ligated to adaptors . . . and then amplified with two rounds of PCR using P5 primer and gene-specific primers (GSPs)." (Ex. 13, Cheng, et al., "Clinical Validation of a Cell-Free DNA Gene Panel," J Mol Diagn, Vol. 21, Issue 4, Pages 632-64, at 634 (July 2019) (emphasis added).)



93. "For each target gene, 16 to 20 primer pairs (GSP1 and GSP2) are designed, covering the complete gene." (Ex. 15, Technical Note, *Archer™ Analysis Variant and CNV detection methods* (PN-MKT- 0041 REV A) at 2.)

94. On information and belief, GSP1 is a mix of at least 10 gene-specific primers. (*See* Ex. 16, LA090.A Protocol, Archer Reveal ctDNA Kit for Illumina, at p. 13 ("Step 5: First PCR . . . 2) Pipette the volume of **GSP1 mix** specified in Product Insert (b) into each First PCR tube.") (emphasis added).)

95. Archer's Reveal ctDNA 28 kit (now called LiquidPlex) "includes **185 targets** [], covering critical regions of 27 genes and the entire coding sequence of *TP53*." (Ex. 13, Cheng, et al., "Clinical Validation of a Cell-Free DNA Gene Panel," J Mol Diagn, Vol. 21, Issue 4, Pages 632-64, at 633-34 (July 2019) (emphasis added).)

96. Thus, on information and belief, Defendants and/or its end-users perform the first PCR to simultaneously amplify between 100 and 5,000 target loci using the first universal primer and between 100 and 5,000 target specific primers in a single reaction volume when using the Accused Products.

97. Thus, on information and belief, Defendants and/or its end-users perform the first PCR to simultaneously amplify between 100 and 1,000 target loci using the first universal primer and between 100 and 1,000 target specific primers in a single reaction volume when using the Accused Products.

98. On information and belief, Defendants and/or its end-users perform the AMP™ process on cell free DNA from tumor when using the Accused Products. For example, Archer's LiquidPlex product is pre-configured to detect 28 gene targets and 12 gene targets in lung focus **tumors**. (Ex. 17 (S-1 filing at p. 116) (emphasis added).)

Pre-configured LiquidPlex products
Solid tumors (gene targets)
LiquidPlex 28 (28)
Lung Focus (12)
Breast Focus (9)
Melanoma Focus (5)

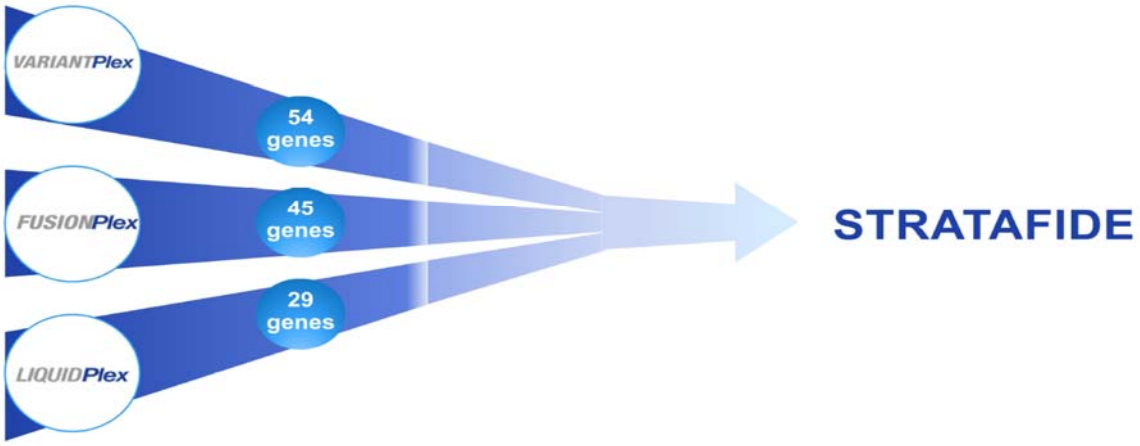
99. "The Archer® LiquidPlex panel for Illumina® is an advanced and user-friendly solution for targeted next-generation sequencing (NGS) of circulating cell-free tumor DNA (ccfDNA/cfDNA/ctDNA) from **28 genes** commonly associated with solid tumor type cancers." (Ex. 18, https://archerdx.com/liquidplex/) (emphasis added).)

100. "Investigators at Massachusetts General Hospital interrogated **110 mutations** using our LiquidPlex product." (Ex. 17 (S-1 filing at p. 121) (emphasis added).)

101. Archer's VariantPlex product is pre-configured to detect **67** gene targets in solid tumor and **75** gene targets in myeloid cancers. (Ex. 17 (S-1 filing at p. 115) (emphasis added).)

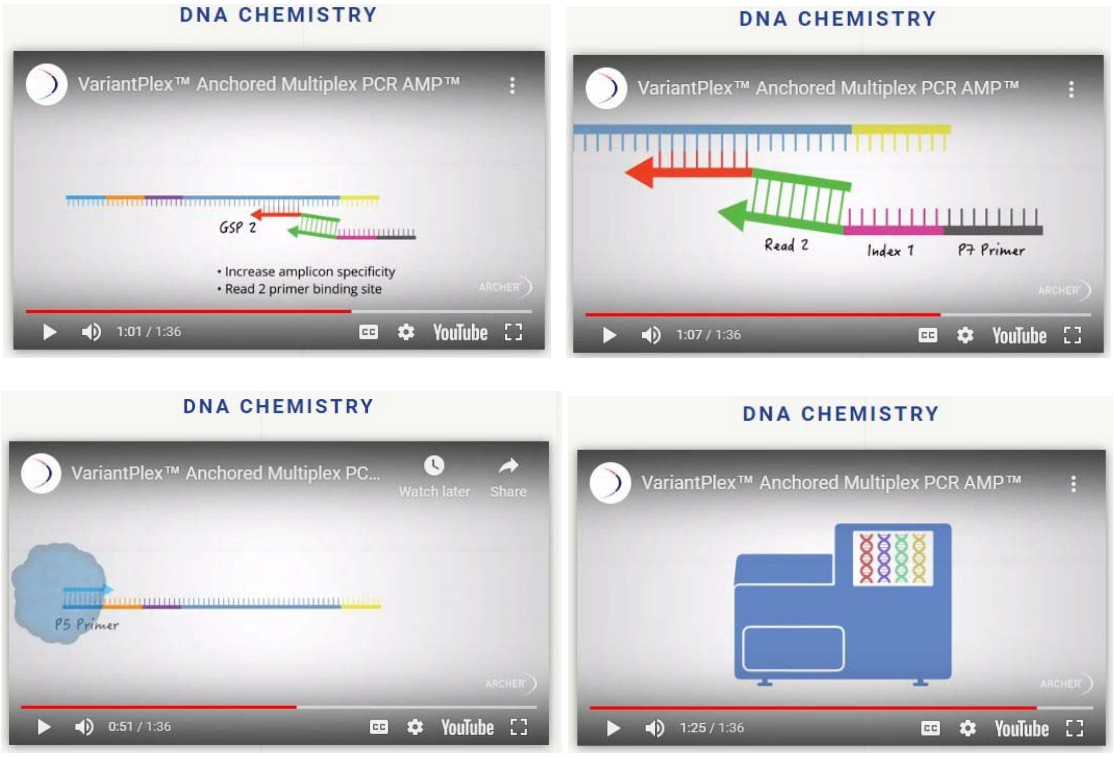
Pre-configured VariantPlex products	
Solid tumors (gene targets)	**Blood cancers (gene targets)**
Solid Tumor (67)	Myleoid (75)
Comprehensive Thyroid & Lung (CTL) (31)	Core Myeloid (37)
Solid tumor Focus (20)	AML Focus (11)
BRCA 1/2 (2)	MPN Focus (13)
P53 (1)	

102. Archer's STRATAFIDE product is used to detect **54** genes from VariantPlex and **29** genes from LiquidPlex. (Ex. 17 (S-1 filing at p. 118) (emphasis added).)

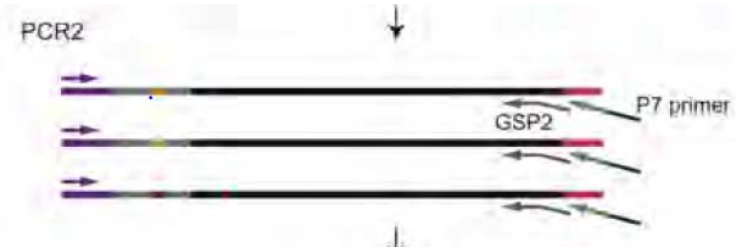


103. Archer's PCM product is "based on a customized LiquidPlex panel" and is used to detect at least "**600 mutations** in a single LiquidPlex panel." (Ex. 17 (S-1 filing at p. 119) (emphasis added).)

104. On information and belief, Defendants and/or its end-users perform a second PCR step using at least 10 target specific primers (GSP2) and another universal primer when using the Accused Products. The video on Archer's AMP webpage states: "The second enrichment amplification uses a different nested gene specific primer to increase amplicon specificity and add a read 2 primer binding site. The second primer is a hybrid that contains a P7 primer and an Index 1 region for MiSeq." The second primer amplifies against the same P5 primer in the adaptor (as shown in the annotated figure below) against which the gene-specific primer in the first PCR amplified. The P5 primer includes a "universal primer binding site." (Ex. 12, https://archerdx.com/technology-platform/technology/.) Both Invitae's and Archer's names and logos are displayed in this webpage.

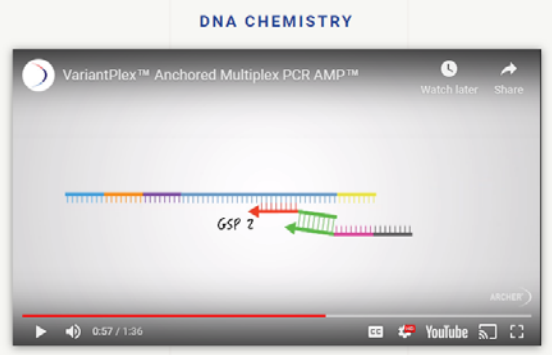


105. Cheng et al, who used the Archer Reveal ctDNA 28 kit (now called LIQUIDPLEX), describes the steps as follows: "Cell-free DNA . . . ligated to adaptors . . . and then amplified with two rounds of PCR using P5 primer and gene-specific primers (GSPs)." (Ex. 13, Cheng, et al., "Clinical Validation of a Cell-Free DNA Gene Panel," J Mol Diagn, Vol. 21, Issue 4, Pages 632-64, at 634 (July 2019) (emphasis added).)



106. On information and belief, in the AMP™ process performed by Defendants and/or its end-users when using the Accused Products, the second PCR step is a one-sided nested PCR. The video on Archer's AMP webpage states that "the second enrichment amplification uses a different nested gene specific primer," GSP2. (Ex. 12, https://archerdx.com/technology-

platform/technology/.) Both Invitae's and Archer's names and logos are displayed in this webpage.



107. "For each target gene, 16 to 20 primer pairs (GSP1 and GSP2) are designed, covering the complete gene." (Ex. 15, Technical Note, *Archer™ Analysis Variant and CNV detection methods* (PN-MKT- 0041 REV A) at 2.)

108. On information and belief, GSP2 is a mix of at least 10 gene-specific primers. (*See* Ex. 16, LA090.A Protocol, Archer Reveal ctDNA Kit for Illumina, at p. 14 ("Step 6: Second PCR . . . 3) Pipette the volume of **GSP2 mix** specified in Product Insert (E) into each Second PCR tube.") (emphasis added).)

109. Archer's Reveal ctDNA 28 kit (now called LiquidPlex) "includes **185 targets** [], covering critical regions of 27 genes and the entire coding sequence of *TP53*." (Ex. 13, Cheng, et al., "Clinical Validation of a Cell-Free DNA Gene Panel," J Mol Diagn, Vol. 21, Issue 4, Pages 632-64, at 633-34 (July 2019) (emphasis added).)

110. Thus, on information and belief, Defendants and/or its end-users perform the second PCR to simultaneously amplify between 100 and 5,000 target loci using the second universal primer and between 100 and 5,000 target specific primers in a single reaction volume when using the Accused Products.

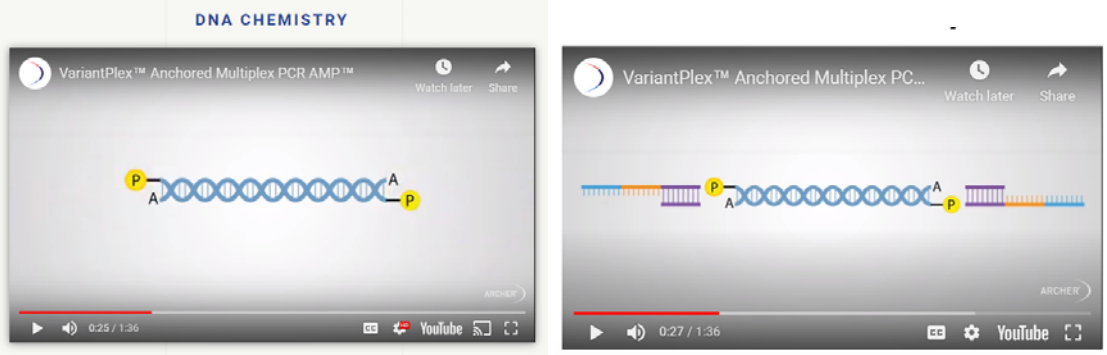
111. Thus, on information and belief, Defendants and/or its end-users perform the second PCR to simultaneously amplify between 100 and 1,000 target loci using the second universal primer and between 100 and 1,000 target specific primers in a single reaction volume when using the Accused Products.

112. On information and belief, Defendants and/or its end-users use a primer with a sequence specific for high throughput sequencers when using the Accused Products. The video on Archer's AMP webpage states that "the second primer is a hybrid that contains a P7 primer and an Index 1 region for MiSeq." (Ex. 12, https://archerdx.com/technology-platform/technology/.)

113. On information and belief, Defendants and/or its end-users perform high-throughput sequencing of the sequences amplified by the above steps when using the Accused Products. (*See e.g.*, Ex. 16, LA090.A Protocol, Archer Reveal ctDNA Kit for Illumina, at p. 17 ("For NextSeq, load sequencing libraries . . . .").)

114. On information and belief, Defendants and/or its end-users performs the AMP™ technology on cell free DNA derived from blood when using the Accused Products. "Anchored Multiplex PCR (AMP™) chemistry is purpose-built to accurately identify both simple and complex genetic mutations . . . from low nucleic acid input in tissue or blood." (Ex. 12, https://archerdx.com/technology-platform/technology/.) Both Invitae's and Archer's names and logos are displayed in this webpage.

115. On information and belief, Defendants and/or its end-users perform the following steps of the AMP™ technology: "[DNA] ends are blunted, a-tailed, and phosphorylated all in one reaction"; the "adaptor is then ligated," when using the Accused Products. (Ex. 12, https://archerdx.com/technology-platform/technology/.) Both Invitae's and Archer's names and logos are displayed in this webpage.



116. On information and belief, Defendants and/or its end-users sequence DNA from multiple samples in a single sequencing lane. "In order to efficiently utilize the throughput of the MiSeq (or other Illumina sequencing platform) . . . multiple samples should be sequenced simultaneously." (Ex. 16, LA090.A Protocol, Archer Reveal ctDNA Kit for Illumina, at p. 8 ("Sample barcodes (i.e. index tags) allow pooled libraries to be sequenced simultaneously thereby enabling maximum sequencing throughput . . .").)

DEFENDANTS' SALE OF THE ACCUSED PRODUCTS TO ITS CUSTOMERS AND THEIR USE OF THE ACCUSED PRODUCTS

117. Defendants sell the Accused Products to end-users who, on information and belief, perform the AMP technology underlying the Accused Products, on cell-free DNA, when they use the Accused Products.

LiquidPlex and VariantPlex

118. LiquidPlex applies AMP to ctDNA to detect and monitor genes commonly associated with cancers. In its website, Archer provides that ctDNA is used as an input in LiquidPlex. (Ex. 19, https://archerdx.com/research-products/solid-tumor-research/.) Both Invitae's and Archer's names and logos are displayed in this webpage.

119. Archer admits that LiquidPlex and VariantPlex "have applications for solid tumors as well as hematological malignancies." Archer's Answer, *Natera, Inc. ArcherDX, Inc.*, Case No. 20-125-LPS, D.I. 21, ¶ 48.

120. VariantPlex applies AMP to ctDNA to "simultaneously detect[] and characterize[] single-nucleotide variants (SNVs), copy number variations (CNVs), and insertions and deletions (indels) in 67 genes associated with solid tumors." (Ex. 20, https://archerdx.com/research-products/solid-tumor-research/variantplex-solid-tumor/.) Both Invitae's and Archer's names and logos are displayed in this webpage.

121. Cell-free DNA is used as an input in VariantPlex. Archer's website provides that "Input cfDNA [is] required" for VariantPlex solid tumor (Ex. 12, https://archerdx.com/research-products/solid-tumor-research/variantplex-solid-tumor/) and VariantPlex Comprehensive Thyroid and Lung products. (Ex. 21, https://archerdx.com/research-products/solid-tumor-research/variantplex-thyroid-and-lung/.) Both Invitae's and Archer's names and logos are displayed in this webpage.

122. Archer admits that LiquidPlex and VariantPlex "are products available for research use only (as opposed to IVDs)." Archer's Answer, *Natera, Inc. ArcherDX, Inc.*, Case No. 20-125-LPS, D.I. 21, ¶ 48.

123. Archer began commercially selling and offering to sell LiquidPlex for research use only on or about September 22, 2016. These sales, offers for sale, and uses do not require FDA

medical device approval, and therefore are not solely for uses reasonably related to any such submission.

124. LiquidPlex is sold as a kit or as component parts so that the assay, on information and belief, is and can be performed by others.

125. Archer has been commercially selling and offering to sell for research use only VariantPlex since on or about 2015. These sales, offers for sale, and uses do not require FDA medical device approval, and therefore are not solely for uses reasonably related to any such submission.

126. VariantPlex is sold as a kit or as component parts so that the assay, on information and belief, is and can be performed by others.

ArcherMET

127. ArcherMET uses AMP to detect certain gene alterations in ctDNA. Archer provides in its website that ArcherMET was approved "to detect MET exon 14 (METex14) skipping alterations in tissue (RNA) and liquid biopsy (ctDNA) from patients with advanced non-small cell lung cancer (NSCLC) . . . ." (Ex. 22, https://archerdx.com/archerdx-receives-approval-for-archermet-companion-diagnostic-for-tepmetko-tepotinib-in-advanced-non-small-cell-lung-cancer-in-japan/.) Both Invitae's and Archer's names and logos are displayed in this webpage.

128. Upon information and belief, ArcherMET is manufactured in the United States and then subsequently shipped overseas for commercial sale, offer for sale, and/or use outside the United States, for example, to Japan. Archer admits that "Archer®MET has been recently approved in Japan." Archer's Answer, *Natera, Inc. ArcherDX, Inc.*, Case No. 20-125-LPS, D.I. 21, ¶ 102.

129. Upon information and belief, ArcherMET is manufactured in the United States. In its Form S-1 filed with the Securities and Exchange Commission on June 5, 2020, Archer does not identify any manufacturing facilities other than its facilities in the United States. Archer states that its products are manufactured and tested in Colorado. (*See e.g.* Ex.17 [S-1 filing] at 145 ("We manufacture our products primarily at our headquarters in Boulder, Colorado." "We also lease approximately 52,465 square feet of office, manufacturing, distribution, lab and freezer space in Louisville, Colorado.").)

130. Archer's manufacturing and operations in the United States consists of raw material procurement, manufacturing, testing, and distribution of the Accused Products. Archer's June 5, 2020 Form S-1 states that the "operations team is responsible for maintaining facilities and equipment per our Quality Management System to meet or exceed ISO 13485:2016 standards to support manufacturing, testing and distribution of our products." (Ex. 17 [S-1 filing] at 130, 145.)

131. On and information, Defendants perform in the United States the claimed method at least during its quality control, internal testing, and validation processes for the Accused Products, including ArcherMET, before it is shipped abroad for sale.

STRATAFIDE AND PCM

132. STRATAFIDE is a pan-solid tumor test designed to identify actionable genomic alterations in tissue or blood samples. In its SEC filing, Archer stated, "STRATAFIDE can be used to detect CNVs, SNVs, InDels and fusions, and utilizes AMP which allows for the addition of biomarker targets to the product without significantly impacting performance." (Ex. 17 at 118.) ctDNA is used as an input in STRATAFIDE. (Ex. 17 at 99.)

133. PCM is a bespoke product that uses AMP for cancer treatment monitoring and recurrence surveillance. PCM "is based on a customized LiquidPlex panel." (Ex. 17 at 119.)

"PCM provides tumor-informed longitudinal analysis of ctDNA found in patient blood where the quantity of ctDNA is a predictor of disease stage and burden. PCM achieves accuracy at low limits of detection by focusing the ctDNA analysis on known patient-specific mutations found in the tumor tissue." (Ex. 17 at 119.)

134. The PCM process includes delivering the "personalized product" "to the laboratory affiliated with the patient's care team" and "[t]he clinician use the personalized product to assess ctDNA taken from non-invasive peripheral blood draws at specified intervals, yielding a quantitative longitudinal view of the cancer's evolution." (Ex.17 at 120.)

135. Upon information and belief, STRATAFIDE and PCM are being and have been commercially sold or offered for sale for research use only ("RUO") basis. In its S-1 filing with the SEC, Archer stated, "Our five **RUO product lines** consist of DNA-based VariantPlex, RNA-based FusionPlex, ctDNA-based LiquidPlex and RNA-based Immunoverse, which we collectively refer to as ArcherPlex, and **Personalized Cancer Monitoring, or PCM**." (Ex. 17, S-1 filing, at 1 (emphasis added).) Archer's April 21, 2020 press release represents that Archer's partner "will identify eight to 10 member institutions that will implement **STRATAFIDE- in a research use only (RUO) capacity** – to participate in a retrospective study . . . ." (Ex. 23 (emphasis added).)

136. These sales, offers for sale, and licensed uses of STRATAFIDE and PCM for RUO basis do not require FDA medical device approval, and therefore Archer has engaged in infringing activities that are not solely for uses reasonably related to any such submission. Archer admits that "RUO [] products, which in contrast to IVD products, do not require FDA approval prior to commercialization." Archer's Answer, *Natera, Inc. ArcherDX, Inc.*, Case No. 20-125 LPS, D.I 21, ¶ 185.

137. The FDA guidance distinguishes uses of RUOs from those related to the submission of data to support IVD FDA approval: RUOs are "intended for use in the conduct of non-clinical laboratory research with goals other than the development of a commercial IVD product, *i.e.*, these products are used to carry out research and are not themselves the object of the research." (Ex. 24 at 7.) On information and belief, Defendants have sold or offered for sale STRATAFIDE and PCM for such uses that are not subject to Section 271(e)(1).

138. Archer states, "[a]s part of an on-going collaboration with University College London and the Francis Crick Institute, we are utilizing PCM to detect low-volume minimal residual disease at high levels of sensitivity to help achieve a more personalized approach to developing cancer treatments." (Ex. 17 at 120.) Such RUO activities are not activities "reasonably related" to Archer obtaining FDA approval of the products as IVDs, as Section 271(e)(1) requires.

139. Upon information and belief, Defendants market their RUO products to their customers for development into laboratory-developed tests ("LDTs"). (Ex. 17 at 78 ("[W]e employed 39 sales representatives in the United States **to market our RUO products** to clinical customers, which include academic and reference laboratories, **for development into laboratory-developed tests**….") (emphasis added).) FDA approval is not required to run laboratory-developed tests. (*Id*. at 135 ("FDA has generally exercised its enforcement discretion and not enforced applicable regulations with respect to...LDTs.").) Such use of the Accused Products as LTDs are infringing activities and are not exempt under Section 271(e)(1).

140. Upon information and belief, Defendants have commercialized PCM and STRATAFIDE for their RUO activities. PCM has been **commercialized since 2019**. (*Id*. at 4 (emphasis added).) Archer generates over $50 million in revenues for its products "through [its]

agreements with [its] customers, including biopharmaceutical companies, academic institutions and molecular labs, who use [their] products for research purposes." (*Id.* at 36, 145.) And "the **commercial success of our RUO products** depends on charging our customers reasonable pricing for the RUO products." (*Id.* at 36 (emphasis added).) This commercial activity is not tied to FDA approval of any product.

141. Upon information and belief, Defendants have commercialized PCM and STRATAFIDE for infringing use in clinical trials. Defendants' supply of PCM and STRATAFIDE for use in clinical trials as research tools is infringing use where PCM and STRATAFIDE themselves are not the subject of FDA approval. (*See* Ex. 25 ("STRATAFIDE identifies actionable genomic alterations in tissue or blood samples, including alterations targeted by emerging therapies undergoing clinical trials, **therapies already recommended in clinical guidelines** such as NCCN, and therapies approved by the FDA."); Ex. 26 ("ArcherDX, Inc., today announced a strategic collaboration with AstraZeneca **to develop assays to support** multiple planned Phase 3 clinical trials for AstraZeneca's targeted immuno-oncology therapeutics.") (emphasis added).)

142. Further, on information and belief, Defendants have engaged in infringing activities as part of their intent to seek IVD approval of STRATAFIDE and PCM that are that are not subject to Section 271(e)(1).

143. Upon information and belief, Defendants have been and will be financially compensated for use of PCM and STRATAFIDE in clinical trials sponsored by third party pharmaceutical companies where such uses are not subject to Section 271(e)(1). Defendants have used, and continue to use, infringing technology to compete against Natera in the bidding process

of various revenue-generating clinical trials by third-party pharmaceutical companies that involve MRD testing.

144. On December 17, 2019, Archer announced the close of a $55 million Series C financing round, the proceeds of which are intended to be used to support the launch of STRATAFIDE and PCM. In a statement from December 17, 2019, Jason Myers, co-founder and chief executive officer of Archer stated that "[t]he proceeds position ArcherDX to, upon approval, launch STRATAFIDE" and "advance our Personalized Cancer Monitoring platform." This financing round was led by Perceptive Advisors, and joined by other investors including Redmile Group, Soleus Capital, Driehaus Capital Management, ArrowMark Partners, Sands Capital, Longwood Fund, PBM Capital and its affiliates, and Boulder Ventures. Upon information and belief, Archer received this financing as a result of its infringing use of Natera's patented technology.

145. Upon information and belief, Defendants have commercially benefited and will benefit from the infringing use of PCM and STRATAFIDE by others. For example, Archer has commercially licensed the technology to Illumina and others for their use. These licensed uses do not require FDA medical device approval and on information and belief, are not solely for uses reasonably related to any submission for FDA approval of the Accused Products. On January 10, 2019, Archer announced a non-exclusive, multi-year partnership with Illumina. This partnership is intended to broaden access of Archer's products. In the January 10, 2019, announcement, Archer Chief Executive Officer Jason Myers stated that the partnership was expected to accelerate the process of creating broad access to testing, shifting away from a handful of centralized sequencing labs to decentralized testing. Myers further stated that the partnership would allow hospitals and local labs to benefit from a "growing share of the cancer diagnostics and monitoring market."

Archer announced on January 10, 2019 that it anticipated that STRATAFIDE would be the first IVD to be marketed under the partnership between Archer and Illumina. Archer also announced that it planned to launch PCM for diagnostic use as part of this commercial partnership. In the January 10, 2019, press release, Dr. Phil Febbo, Chief Medical Officer of Illumina, stated that Archer and Illumina were "pleased to take this next step in [their] commercial partnership to support expanding access to leading- edge genomic cancer management to more patients, in more communities, to improve patient outcomes." Through such collaboration, Defendants have and will continue to make PCM and STRATAFIDE available for infringing use by others and inure commercial benefits from such infringing uses.

146. Upon information and belief, STRATAFIDE and PCM are being put to infringing use in the on-going Tracking Launch Cancer Evolution Through Treatment (TRACERx) study led by Dr. Charles Swanton and Dr. Christopher Abbosh. On March 28, 2019, Archer announced that it entered into this research collaboration agreement with the University College London ("UCL") and the Francis Crick Institute. This UCL-sponsored study uses infringing AMP technology to expand on findings from an earlier clinical study by developing patient-specific assays to detect low volume minimal residual disease at high levels of sensitivity. Uses of STRATAFIDE and PCM for research use only purposes or as a research tool in the UCL-sponsored study are examples of infringing uses that are outside the § 271(e)(1) exemption.

147. Archer admits that it received the FDA's Breakthrough Device Designation for STRATAFIDE in December 2018. Archer's Answer, *Natera, Inc. ArcherDX, Inc.*, Case No. 20-125-LPS, D.I 21 at ¶ 108. Defendants intend to sell the product for diagnostic use immediately upon approval, which it "expects" in 2021, according to its June 5, 2020 S-1. In submitting an application for STRATAFIDE to the FDA, Archer had to describe the product with specificity. In

particular, upon information and belief, Archer would have had to describe the specific intended use of the product, the specific primers used, and the specific genetic alterations targeted.

148. Archer admits that it received the FDA's Breakthrough Device Designation for PCM in January 2020. Archer's Answer, *Natera, Inc. ArcherDX, Inc.*, Case No. 20-125-LPS, D.I. 21 at ¶ 109. Defendants intend to sell the product for diagnostic use immediately upon approval. In submitting an application for PCM to the FDA, Archer had to describe the product with specificity. In particular, upon information and belief, Archer would have had to describe the specific intended use of the product, the specific primers used, and the specific genetic alterations targeted.

149. On information and belief, STRATAFIDE is sold as a kit or as component parts so that the assay is and can be performed by others.

150. On information and belief, PCM is sold as a kit or as component parts so that the assay is and can be performed by others.

151. Defendants' development of its Accused Products has been aided by access to and use of Natera's innovative research and development.

152. For example, Natera worked with Dr. Charles Swanton at the UCL to validate its Signatera® technology in the TRACERx lung cancer study. The study involves analyzing the intratumor heterogeneity of lung tumors in approximately 850 patients and the tracking its evolution from diagnosis to relapse. Dr. Swanton, in his role as the principal investigator, senior researcher, and author of the study, led the development of bespoke personalized assays to target variants selected after the sequencing of primary tumors. After surgery, patients were followed to track clonal and subclonal evolution of the disease based on ctDNA measurements of blood samples. Over twenty PCR assays were designed and analyzed for each specimen, without

splitting plasma samples, so that multiple subclones were tracked simultaneously. Subsequent to that collaboration, Archer announced that it was collaborating with Dr. Swanton on that same study and used similar methodology. A January 14, 2020, Archer press release states that Archer has an "on-going collaboration" with Dr. Swanton, who is now "utilizing ArcherDX's technology … to help achieve" the goals of the TRACERx study.

153. Upon information and belief, Defendants were able to develop its Accused Products, including its STRATAFIDE and PCM products, as a direct result of unlawful use of Natera's innovative technology.

154. FusionPlex is a targeted sequencing assay that simultaneously detects and identifies fusions and other mutations associated with cancers.

155. Defendants have been commercially selling and offering to sell FusionPlex for investigational and research use only. These sales, offers for sale, and uses do not require FDA medical device approval, and therefore are not solely for uses reasonably related to any such submission. For example, Archer announced on January 10, 2019 that the partnership between Archer and Illumina expands upon a prior agreement between the two companies to co-market and co-promote FusionPlex in markets outside of the United States. On June 6, 2016, Archer had announced a co-marketing and distribution agreement with Illumina under which Illumina would market and promote FusionPlex "through its global commercial channels." Under the 2016 agreement, Archer would sell its products in the United States while Illumina would distribute FusionPlex in international markets on a non-exclusive basis.

156. FusionPlex is sold as a kit or as component parts so that the assay can be performed by others.

157. Defendants are a direct competitor of Natera in the market for tumor monitoring. For example, Archer identifies Natera as "[o]ne of our competitors. . . ." (Ex. 17, S-1 filing, at 7, 16.)

158. Defendants have knowledge of the '814 Patent at least as early as January 27, 2020.

159. Defendants have knowledge of the '172 Patent at least as early as the date of this first amended complaint.

160. Defendants have knowledge of the '482 Patent at least as early as the date of this first amended complaint.

161. Defendants have knowledge of the '708 Patent at least as early as the date of this first amended complaint.

162. Defendants have knowledge of the '220 Patent at least as early as the date of the complaint filed on August 6, 2020.

163. On information and belief, Invitae, as part of its merger with ArcherDX, performed this year extensive due diligence on this lawsuit, including using counsel to understand the nature of the allegations. As a result, on information and belief, Invitae is fully knowledgeable about the asserted patents and ArcherDX's accused infringing activities as set forth in Natera's earlier filed complaints. Nonetheless, defendants continue to infringe in blatant disregard of Natera's issued patents as defendants execute on Invitae's publicly stated intent and plan to expand into the oncology markets.

COUNT I
(Infringement of U.S. Patent No. 10,538,814)

164. Natera repeats and realleges the foregoing paragraphs as if fully set forth herein.

165. Natera is the owner of the '814 Patent, which was duly and legally issued by the USPTO on January 21, 2020.

166. Defendants have infringed and continue to infringe at least one claim of the '814 Patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States and without authority the tests of the cfDNA Accused Products.

167. Defendants have infringed and continue to infringe at least one claim of the '814 Patent pursuant to 35 U.S.C. § 271(b), literally or under the doctrine of equivalents, by selling and offering for sale in the United States the cfDNA Accused Products and instructing end-users through instructional materials, product manuals, and technical materials, disseminating promotional/marketing materials that describe the workflows and use of those tests, and otherwise instructing end-users to use the cfDNA Accused Products to infringe at least claim of the '814 Patent. At least as of the date hereof, Defendants sell and distribute the cfDNA Accused Products with the knowledge and specific intent that these instructions will cause end-users to infringe at least one claim of the '814 Patent, and therefore Defendants induce end-users to use the cfDNA Accused Products in methods that directly infringe at least one claim of the '814 Patent. Defendant Invitae further infringes under 35 U.S.C. § 271(b) for any use of the patented method by Archer or other acts of infringement as such activities are conducted with the knowledge, direction and specific intent that Archer shall perform them.

168. Defendants have infringed and continue to infringe at least one claim of the '814 Patent pursuant to 35 U.S.C. § 271(c), literally or under the doctrine of equivalents, by offering to sell or selling the cfDNA Accused Products within the United States for use by end-users in practicing at least one of the claimed methods of the '814 Patent. The cfDNA Accused Products each constitutes a material part of the invention of the '814 Patent, and, at least as of the date

hereof, Defendants know the cfDNA Accused Products to be especially made or especially adapted for use in infringing the '814 Patent. Furthermore, none of the cfDNA Accused Products is a staple article or commodity of commerce suitable for substantial noninfringing use. Defendants sell and offer for sale the cfDNA Accused Products with the knowledge and specific intent that its instructions and workflows will cause end-users to use the products to infringe at least one claim of the '814 Patent.

169. Defendants' infringement has damaged and will continue to damage Natera, which is entitled to recover the damages resulting from Defendants' wrongful acts in an amount to be determined at trial, and in any event no less than a reasonable royalty.

170. Moreover, Defendants' infringement has caused, and will continue to cause, irreparable injury to Natera, for which damages are an inadequate remedy, unless Defendants are enjoined from any and all activities that would infringe the claims of the '814 Patent.

COUNT II
(Declaratory Judgment of Infringement of U.S. Patent No. 10,538,814)

171. Natera repeats and realleges the foregoing paragraphs as if fully set forth herein.

172. Archer has sought and received the FDA's Breakthrough Device designation for at least some of the cfDNA Accused Products, including Stratafide and PCM. Natera believes, and on that basis alleges, that Defendants intend to engage in the commercial manufacture, use, offer for sale, and sale of the cfDNA Accused Products if and when it receives FDA approval to do so.

173. An actual, substantial, and justiciable controversy has arisen and now exists between the parties concerning whether, *inter alia*, the manufacture, use, offer for sale, sale, and/or importation of the cfDNA Accused Products has or will infringe one or more claims of the '814 Patent.

174. Natera is entitled to a judicial declaration that Defendants have infringed or will infringe, directly and/or indirectly, literally and/or under the doctrine of equivalents, one or more claims of the ’814 Patent.

175. Defendants’ infringement has damaged and will continue to damage Natera, which is entitled to recover the damages resulting from Defendants’ wrongful acts in an amount to be determined at trial, and in any event no less than a reasonable royalty.

176. Moreover, Defendants’ infringement has caused, and will continue to cause, irreparable injury to Natera, for which damages are an inadequate remedy, unless Defendants are enjoined from any and all activities that would infringe the claims of the ’814 Patent.

COUNT III
(Infringement of U.S. Patent No. 10,557,172)

177. Natera repeats and realleges the foregoing paragraphs as if fully set forth herein.

178. Natera is the owner of the ’172 Patent, which was duly and legally issued by the USPTO on February 11, 2020.

179. Defendants have infringed and continue to infringe at least one claim of the ’172 Patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States and without authority the tests of the cfDNA Accused Products.

180. Defendants have infringed and continue to infringe at least one claim of the ’172 Patent pursuant to 35 U.S.C. § 271(b), literally or under the doctrine of equivalents, by selling and offering for sale in the United States the cfDNA Accused Products and instructing end-users through instructional materials, product manuals, and technical materials, disseminating promotional/marketing materials that describe the workflows and use of those tests, and otherwise instructing end-users to use the cfDNA Accused Products to infringe at least claim of the ’172 Patent. At least as of the date hereof, Defendants sell and distribute the cfDNA Accused

Products with the knowledge and specific intent that these instructions will cause end-users to infringe at least one claim of the '172 Patent, and therefore Defendants induce end-users to use the cfDNA Accused Products in methods that directly infringe at least one claim of the '172 Patent. Defendant Invitae further infringes under 35 U.S.C. § 271(b) for any use of the patented method by Archer or other acts of infringement as such activities are conducted with the knowledge, direction and specific intent that Archer shall perform them.

181. Defendants have infringed and continue to infringe at least one claim of the '172 Patent pursuant to 35 U.S.C. § 271(c), literally or under the doctrine of equivalents, by offering to sell or selling the cfDNA Accused Products within the United States for use by end-users in practicing at least one of the claimed methods of the '172 Patent. The cfDNA Accused Products each constitutes a material part of the invention of the '172 Patent, and, at least as of the date hereof, Defendants know the cfDNA Accused Products to be especially made or especially adapted for use in infringing the '172 Patent. Furthermore, none of the cfDNA Accused Products is a staple article or commodity of commerce suitable for substantial noninfringing use. Defendants sell and offer for sale the cfDNA Accused Products with the knowledge and specific intent that its instructions and workflows will cause end-users to use the products to infringe at least one claim of the '172 Patent.

182. Defendants' infringement has damaged and will continue to damage Natera, which is entitled to recover the damages resulting from Defendants' wrongful acts in an amount to be determined at trial, and in any event no less than a reasonable royalty.

183. Moreover, Defendants' infringement has caused, and will continue to cause, irreparable injury to Natera, for which damages are an inadequate remedy, unless Defendants are enjoined from any and all activities that would infringe the claims of the '172 Patent.

COUNT IV
(Declaratory Judgment of Infringement of U.S. Patent No. 10,557,172)

184. Natera repeats and realleges the foregoing paragraphs as if fully set forth herein.

185. Archer has sought and received the FDA's Breakthrough Device designation for at least some of the cfDNA Accused Products, including Stratafide and PCM. Natera believes, and on that basis alleges, that Defendants intend to engage in the commercial manufacture, use, offer for sale, and sale of the cfDNA Accused Products if and when they receive FDA approval to do so.

186. An actual, substantial, and justiciable controversy has arisen and now exists between the parties concerning whether, *inter alia*, the manufacture, use, offer for sale, sale, and/or importation of the cfDNA Accused Products has or will infringe one or more claims of the '172 Patent.

187. Natera is entitled to a judicial declaration that Defendants have infringed or will infringe, directly and/or indirectly, literally and/or under the doctrine of equivalents, one or more claims of the '172 Patent.

188. Defendants' infringement has damaged and will continue to damage Natera, which is entitled to recover the damages resulting from Defendants' wrongful acts in an amount to be determined at trial, and in any event no less than a reasonable royalty.

189. Moreover, Defendants' infringement has caused, and will continue to cause, irreparable injury to Natera, for which damages are an inadequate remedy, unless Defendants are enjoined from any and all activities that would infringe the claims of the '172 Patent.

COUNT V
(Infringement of U.S. Patent No. 10,590,482)

190. Natera repeats and realleges the foregoing paragraphs as if fully set forth herein.

191. Natera is the owner of the '482 Patent, which was duly and legally issued by the USPTO on March 17, 2020.

192. Defendants have infringed and continue to infringe at least one claim of the '482 Patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States and without authority the tests of the cfDNA Accused Products.

193. Defendants have infringed and continue to infringe at least one claim of the '482 Patent pursuant to 35 U.S.C. § 271(b), literally or under the doctrine of equivalents, by selling and offering for sale in the United States the cfDNA Accused Products and instructing end-users through instructional materials, product manuals, and technical materials, disseminating promotional/marketing materials that describe the workflows and use of those tests, and otherwise instructing end-users to use the cfDNA Accused Products to infringe at least claim of the '482 Patent. At least as of the date hereof, Defendants sell and distribute the cfDNA Accused Products with the knowledge and specific intent that these instructions will cause end-users to infringe at least one claim of the '482 Patent, and therefore Defendants induce end-users to use the cfDNA Accused Products in methods that directly infringe at least one claim of the '482 Patent. Defendant Invitae further infringes under 35 U.S.C. § 271(b) for any use of the patented method by Archer or other acts of infringement as such activities are conducted with the knowledge, direction and specific intent that Archer shall perform them.

194. Defendants have infringed and continue to infringe at least one claim of the '482 Patent pursuant to 35 U.S.C. § 271(c), literally or under the doctrine of equivalents, by offering to sell or selling the cfDNA Accused Products within the United States for use by end-users in practicing at least one of the claimed methods of the '482 Patent. The cfDNA Accused Products each constitutes a material part of the invention of the '482 Patent, and, at least as of the date

hereof, Defendants know the cfDNA Accused Products to be especially made or especially adapted for use in infringing the '482 Patent. Furthermore, none of the cfDNA Accused Products is a staple article or commodity of commerce suitable for substantial noninfringing use. Defendants sell and offer for sale the cfDNA Accused Products with the knowledge and specific intent that its instructions and workflows will cause end-users to use the products to infringe at least one claim of the '482 Patent.

195. Defendants' infringement has damaged and will continue to damage Natera, which is entitled to recover the damages resulting from Defendants' wrongful acts in an amount to be determined at trial, and in any event no less than a reasonable royalty.

196. Moreover, Defendants' infringement has caused, and will continue to cause, irreparable injury to Natera, for which damages are an inadequate remedy, unless Defendants are enjoined from any and all activities that would infringe the claims of the '482 Patent.

COUNT VI
(Declaratory Judgment of Infringement of U.S. Patent No. 10,590,482)

197. Natera repeats and realleges the foregoing paragraphs as if fully set forth herein.

198. Archer has sought and received the FDA's Breakthrough Device designation for at least some of the cfDNA Accused Products, including Stratafide and PCM. Natera believes, and on that basis alleges, that Defendants intend to engage in the commercial manufacture, use, offer for sale, and sale of the cfDNA Accused Products if and when it receives FDA approval to do so.

199. An actual, substantial, and justiciable controversy has arisen and now exists between the parties concerning whether, *inter alia*, the manufacture, use, offer for sale, sale, and/or importation of the cfDNA Accused Products has or will infringe one or more claims of the '482 Patent.

200. Natera is entitled to a judicial declaration that Defendants have infringed or will infringe, directly and/or indirectly, literally and/or under the doctrine of equivalents, one or more claims of the ’482 Patent.

201. Defendants’ infringement has damaged and will continue to damage Natera, which is entitled to recover the damages resulting from Defendants’ wrongful acts in an amount to be determined at trial, and in any event no less than a reasonable royalty.

202. Moreover, Defendants’ infringement has caused, and will continue to cause, irreparable injury to Natera, for which damages are an inadequate remedy, unless Defendants are enjoined from any and all activities that would infringe the claims of the ’482 Patent.

COUNT VII
(Infringement of U.S. Patent No. 10,597,708)

203. Natera repeats and realleges the foregoing paragraphs as if fully set forth herein.

204. Natera is the owner of the ’708 Patent, which was duly and legally issued by the USPTO on March 24, 2020.

205. Defendants have infringed and continue to infringe at least one claim of the ’708 Patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States and without authority the tests of the Accused Products.

206. Defendants have infringed and continue to infringe at least one claim of the ’ 708 Patent pursuant to 35 U.S.C. § 271(b), literally or under the doctrine of equivalents, by selling and offering for sale in the United States the Accused Products and instructing end-users through instructional materials, product manuals, and technical materials, disseminating promotional/marketing materials that describe the workflows and use of those tests, and otherwise instructing end-users to use the Accused Products to infringe at least claim of the ’ 708 Patent. At least as of the date hereof, Defendants sell and distribute the Accused Products with

the knowledge and specific intent that these instructions will cause end-users to infringe at least one claim of the '708 Patent, and therefore Defendants induce end-users to use the Accused Products in methods that directly infringe at least one claim of the '708 Patent. Defendant Invitae further infringes under 35 U.S.C. § 271(b) for any use of the patented method by Archer or other acts of infringement as such activities are conducted with the knowledge, direction and specific intent that Archer shall perform them.

207. Defendants have infringed and continue to infringe at least one claim of the '708 Patent pursuant to 35 U.S.C. § 271(c), literally or under the doctrine of equivalents, by offering to sell or selling the Accused Products within the United States for use by end-users in practicing at least one of the claimed methods of the '708 Patent. The Accused Products each constitute a material part of the invention of the '708 Patent, and, at least as of the date hereof, Defendants know the Accused Products to be especially made or especially adapted for use in infringing the '708 Patent. Furthermore, none of the Accused Products is a staple article or commodity of commerce suitable for substantial noninfringing use. Defendants sell and offer for sale the Accused Products with the knowledge and specific intent that its instructions and workflows will cause end-users to use the products to infringe at least one claim of the '708 Patent.

208. Defendants' infringement has damaged and will continue to damage Natera, which is entitled to recover the damages resulting from Defendants' wrongful acts in an amount to be determined at trial, and in any event no less than a reasonable royalty.

209. Moreover, Defendants' infringement has caused, and will continue to cause, irreparable injury to Natera, for which damages are an inadequate remedy, unless Defendants are enjoined from any and all activities that would infringe the claims of the '708 Patent.

COUNT VIII
(Declaratory Judgment of Infringement of U.S. Patent No. 10,597,708)

210. Natera repeats and realleges the foregoing paragraphs as if fully set forth herein.

211. Archer has sought and received the FDA's Breakthrough Device designation for at least some of the Accused Products, including Stratafide and PCM. Natera believes, and on that basis alleges, that Defendants intend to engage in the commercial manufacture, use, offer for sale, and sale of the Accused Products if and when it receives FDA approval to do so.

212. An actual, substantial, and justiciable controversy has arisen and now exists between the parties concerning whether, *inter alia*, the manufacture, use, offer for sale, sale, and/or importation of the Accused Products has or will infringe one or more claims of the '708 Patent.

213. Natera is entitled to a judicial declaration that Defendants have infringed or will infringe, directly and/or indirectly, literally and/or under the doctrine of equivalents, one or more claims of the '708 Patent.

214. Defendants' infringement has damaged and will continue to damage Natera, which is entitled to recover the damages resulting from Defendants' wrongful acts in an amount to be determined at trial, and in any event no less than a reasonable royalty.

215. Moreover, Defendants' infringement has caused, and will continue to cause, irreparable injury to Natera, for which damages are an inadequate remedy, unless Defendants are enjoined from any and all activities that would infringe the claims of the '708 Patent.

COUNT IX
(Infringement of U.S. Patent No. 10,731,220)

216. Natera repeats and realleges the foregoing paragraphs as if fully set forth herein.

217. Defendants have infringed and continue to infringe at least one claim of the '220 Patent, pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States and without authority the tests of the Accused Products.

218. Defendants have infringed and continue to infringe at least one claim of the '220 Patent pursuant to 35 U.S.C. § 271(b), literally or under the doctrine of equivalents, by selling and offering for sale in the United States the Accused Products and instructing end-users through instructional materials, product manuals, and technical materials, disseminating promotional/marketing materials that describe the workflows and use of those tests, and otherwise instructing end-users to use the Accused Products to infringe at least one claim of the '220 Patent.

219. At least as of the date hereof, Defendants sell and distribute the Accused Products with the knowledge and specific intent that these instructions will cause end-users to infringe at least one claim of the '220 Patent, and therefore Defendants induce end-users to use the Accused Products in methods that directly infringe at least one claim of the '220 Patent. Defendant Invitae further infringes under 35 U.S.C. § 271(b) for any use of the patented method by Archer or other acts of infringement as such activities are conducted with the knowledge, direction and specific intent that Archer shall perform them.

220. Defendants have infringed and continue to infringe at least one claim of the '220 Patent pursuant to 35 U.S.C. § 271(c), literally or under the doctrine of equivalents, by offering to sell or selling the Accused Products within the United States for use by end-users in practicing at least one of the claimed methods of the '220 Patent. The Accused Products each constitutes a material part of the invention of the '220 Patent, and, at least as of the date hereof, Defendants know the Accused Products to be especially made or especially adapted for use in infringing the '220 Patent. Furthermore, none of the Accused Products is a staple article or commodity of commerce suitable for substantial noninfringing use. Defendants sell and offer for sale the Accused Products with the knowledge and specific intent that its instructions and workflows will cause end-users to use the products to infringe at least one claim of the '220 Patent.

221. Defendants' infringement has damaged and will continue to damage Natera, which is entitled to recover the damages resulting from Defendants' wrongful acts in an amount to be determined at trial, and in any event no less than a reasonable royalty.

222. Moreover, Defendants' infringement has caused, and will continue to cause, irreparable injury to Natera, for which damages are an inadequate remedy, unless Defendants are enjoined from any and all activities that would infringe the claims of the '220 Patent.

COUNT X
(Declaratory Judgment of Infringement of U.S. Patent No. 10,731,220)

223. Natera repeats and realleges the foregoing paragraphs as if fully set forth herein.

224. Defendants have infringed and continue to infringe at least one claim of the '220 Patent, pursuant to 35 U.S.C. § 271(a), (b), and/or (c), including from RUO, LDT, and research tool activities using STRATAFIDE and PCM.

225. Archer admits that it has received the FDA's Breakthrough Device designation for STRATAFIDE and PCM. Natera believes, and on that basis alleges, that Defendants intend to engage in the commercial manufacture, use, offer for sale, and sale of the Accused Products as in vitro diagnostic products (IVDs) if and when it receives FDA approval to do so.

226. The prospects for FDA approval is not speculative. Archer states in its S-1 filing to the SEC: "We expect to launch STRATAFIDE as a regulated device in 2021." (Ex. 17, at 4, 77.)

227. An actual, substantial, and justiciable controversy has arisen and now exists between the parties concerning whether, *inter alia*, the manufacture, use, offer for sale, sale, and/or importation of the Accused Products has or will infringe one or more claims of the '220 Patent.

228. The controversy is immediate. Archer stated to the SEC that it expects to submit its FDA application this year and may get FDA marketing authorization "within 90 days" of

submission. (Ex. 17 at 119 ("We plan to submit our initial companion diagnostic claims on STRATAFIDE for FDA approval in 2020, including 510(k) filings or PMA filings"); Ex. 17 at 137 ("By statute, the FDA is required to complete its review of a 510(k) notification within 90 days of receiving the 510(k) notification.").)

229. Archer further states that it expects a "faster review through priority review" by the FDA since "STRATAFIDE and PCM have both received Breakthrough Device designation from the FDA." (Ex. 17 at 1, 77, 96.)

230. Archer has engaged in "meaningful preparation" for "making, launch, and use of" STRATAFIDE and PCM for clinical diagnostic uses after FDA approval, sufficient to meet the "immediacy" requirement. Archer stated in its S-1 filing, "We have devoted a substantial portion of our resources to the development and commercialization of STRATAFIDE, a . . . IVD" and "expect to expand this commercial presence ahead of regulatory clearance and/or approvals of our pipeline products." (Ex. 17 at 13.)

231. The controversy is real. The infringing AMP technology is "substantially fixed" for STRATAFIDE and PCM and in fact, are already being commercially supplied for RUO activities.

232. Natera is entitled to a judicial declaration that Defendants have infringed or will infringe, directly and/or indirectly, literally and/or under the doctrine of equivalents, one or more claims of the '220 Patent.

233. Defendants' infringement has damaged and will continue to damage Natera, which is entitled to recover the damages resulting from Defendants' wrongful acts in an amount to be determined at trial, and in any event no less than a reasonable royalty.

234. Moreover, Defendants' infringement has caused, and will continue to cause, irreparable injury to Natera, for which damages are an inadequate remedy, unless Defendants are enjoined from any and all activities that would infringe the claims of the '220 Patent.

PRAYER FOR RELIEF

WHEREFORE, Natera prays for a judgment in its favor and against Defendants and respectfully request the following relief:

1. A judgment that Defendants directly infringe, induce infringement, and contributorily infringe the Asserted Patents.

2. An order enjoining Defendants and their officers, directors, agents, servants, affiliates, employees, divisions, branches, subsidiaries, parents, and all others acting in active concert therewith from further infringement of the Asserted Patents.

3. Damages or other monetary relief, including, but not limited to, costs and pre and post-judgment interest, to Natera;

4. A determination that this is an exceptional case under 35 U.S.C. § 285 and an award of attorneys' fees and costs to Natera in this action;

5. Costs and expenses in this action;

6. An order awarding Natera any such other relief as the Court may deem just and proper under the circumstances.

JURY DEMAND

Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, Natera hereby demands a jury trial as to all issues so triable.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Derek J. Fahnestock

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January 12, 2021

CERTIFICATE OF SERVICE

I hereby certify that on January 12, 2021, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on January 12, 2021, upon the following in the manner indicated:

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